(19)日本国特許庁（ＪＰ）　(12)**公開特許公報**（Ａ）　(11)特許出願公開番号

特開平11－169690

(43)公開日　平成11年(1999)６月29日

(51)Int.Cl.[6]	識別記号	ＦＩ	
Ｂ０１Ｄ　69/02		Ｂ０１Ｄ　69/02	
Ａ６１Ｍ　1/16	５００	Ａ６１Ｍ　1/16	５００
Ｂ０１Ｄ　71/40		Ｂ０１Ｄ　71/40	
71/68		71/68	

審査請求　未請求　請求項の数４　ＦＤ　（全 ９ 頁）

(21)出願番号　特願平9－363136

(22)出願日　平成９年(1997)12月15日

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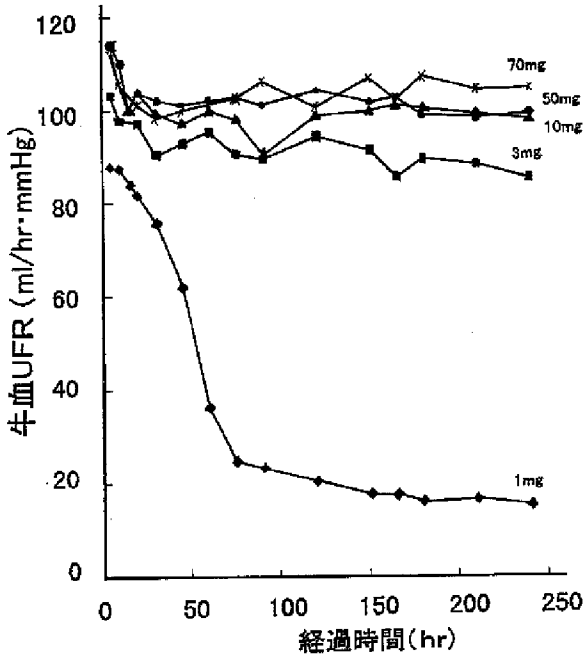
(54)【発明の名称】　血液浄化膜

(57)【要約】

【課題】　親水性高分子の漏出阻止性と良好な血液適合性とを両立させ得る血液浄化膜を提供する。

【解決手段】　ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材とした疎水性高分子膜の表面に、ポリビニルピロリドンの水溶液を疎水性高分子膜に接触させ、疎水性高分子膜１平方メートルあたり３ミリグラム以上５０ミリグラム以下のポリビニルピロリドンを付着保持せしめた。



【特許請求の範囲】
【請求項１】　親水性高分子を疎水性高分子膜に保持させた血液浄化膜であって、
疎水性高分子膜１平方メートルあたりの親水性高分子の保持量を、３ミリグラム以上５０ミリグラム以下としたことを特徴とする血液浄化膜。
【請求項２】　前記親水性高分子がポリビニルピロリドンであることを特徴とする請求項１記載の血液浄化膜。
【請求項３】　親水性高分子の溶液を疎水性高分子膜に接触させることにより、親水性高分子を疎水性高分子膜に物理的に付着保持せしめたことを特徴とする請求項１又は請求項２記載の血液浄化膜。
【請求項４】　前記疎水性高分子膜は、ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材としていることを特徴とする請求項１から３のいずれかに記載の血液浄化膜。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、血液浄化療法に用いる血液浄化膜に関する。
【０００２】
【従来の技術】血液浄化療法は、血液中の不要物質（尿毒症物質等）を除去する治療方法である。この血液浄化療法では、半透膜や限外濾過膜を血液浄化膜として用いている。例えば、５０００本～１００００本程度の中空糸膜（血液浄化膜を中空糸状に紡糸したもの）を束ねた中空糸束を、ケーシング内に装填して構成した血液浄化器を用いている。
【０００３】この血液浄化療法には、血液透析療法、血液濾過療法、あるいは血液濾過透析療法等がある。血液透析療法では、血液浄化器における中空糸膜の内表面側に血液を流すとともに外表面側に透析液を流し、中空糸膜を介して血液と透析液とを接触させ、拡散により尿毒症物質及び体内の過剰な水分を除去する。血液濾過療法では、血液浄化器における中空糸膜の内表面側に血液を流すことにより、尿毒症物質を濾別除去する。また、血液濾過透析療法では、血液濾過療法と血液透析療法の両方の特性、即ち、濾過と拡散によって尿毒症物質と体内の過剰な水分を除去する。
【０００４】この血液浄化療法で用いる血液浄化膜としては、セルロースに代表される親水性高分子や、ポリスルホン、ポリエステルに代表される疎水性高分子が好適に用いられている。機械的強度に優れ、生体への影響が少ないからである。しかしながら、一般的に、疎水性材料（高分子）を血液浄化膜として使用するためには、この疎水性材料に親水性を付与している場合が多い。これは、疎水性材料のみから製造された膜の表面には、タンパク質や血小板等の血液成分の付着が起こりやすく、使用中における膜透過性能の低下等が問題になるからである。即ち、疎水性材料のみから製造された膜では、良好な血液適合性が得難いからである。
【０００５】そして、疎水性材料から、親水性の付与された膜を製造する方法としては、製膜原液中に親水性高分子を添加して製膜する方法が一般的になされている。この方法は、元来、疎水性材料から血液成分が分離可能な膜構造を形成するために、親水性高分子を開孔剤として使用していたものが、結果的に疎水性材料に親水性を付加して製膜することが出来たものである。この方法において、製膜原液中に添加する親水性高分子としては、例えば、ポリビニルピロリドンが好適に用いられている。即ち、このポリビニルピロリドンを製膜原液に添加して紡糸することにより、血液成分が適正に分離可能な膜構造を形成すると共に、疎水性材料に親水性を付与することができる。
【０００６】この方法では、血液成分を適正に分離できるような膜構造を形成するために、比較的多量の親水性高分子を添加する必要がある。このため、作製した血液浄化膜には比較的多量の親水性高分子が残存しており、この残存した親水性高分子の漏出を阻止する処理が行われている。例えば、親水性高分子を熱、放射線、薬品等で架橋させたりして漏出を防いでいる。
【０００７】
【発明が解決しようとする課題】しかしながら、上記したように、過剰な親水性高分子が残存しているため、親水性高分子の漏出を阻止する処理を施したとしても、親水性高分子の漏出を確実に阻止することが困難であった。従って、漏出した親水性高分子が体内に混入する虞があった。そして、体内に混入した親水性高分子が生体へ何らかの影響を与える可能性があるため、親水性高分子の体内への混入をできる限り除去することが望ましい。
【０００８】本発明は、この様な事情に鑑みてなされたものであり、良好な血液適合性が得られ、尚且つ、親水性高分子の漏出をも阻止し得る血液浄化膜を提供することを目的とする。
【０００９】
【課題を解決するための手段】上記した目的を達成するため、本発明における請求項１記載のものは、親水性高分子を疎水性高分子膜に保持させた血液浄化膜であって、疎水性高分子膜１平方メートルあたりの親水性高分子の保持量を、３ミリグラム以上５０ミリグラム以下としたことを特徴とする。
【００１０】また、請求項２記載のものは、請求項１記載の構成に加えて、前記親水性高分子がポリビニルピロリドンであることを特徴とする血液浄化膜である。
【００１１】また、請求項３記載のものは、請求項１又は請求項２記載の構成に加えて、親水性高分子の溶液を疎水性高分子膜に接触させることにより、親水性高分子を疎水性高分子膜に物理的に付着保持せしめたことを特徴とする血液浄化膜である。

【００１２】また、請求項４記載のものは、請求項１から３のいずれかに記載の構成に加えて、前記疎水性高分子膜は、ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材としていることを特徴とする血液浄化膜である。

【００１３】

【発明の実施の形態】以下、本発明の実施の形態を、図面を参照して説明する。まず、本発明の血液浄化膜を用いた血液浄化器について説明する。ここで、図１は、血液浄化器１を断面にして示した図であり、図２は、ケーシング２の端部における中空糸束の切断面を示した図である。

【００１４】図１に示すように、血液浄化器１は、ケーシング２と、このケーシング２に対して着脱自在に螺合する注入側血液ポート３及び排出側血液ポート４とから構成してある。ケーシング２は、ポリカーボネイトにより形成された円筒状部材である。そして、このケーシング２の側面であって排出側血液ポート４側の端部には透析液の流入口５を形成してあり、注入側血液ポート３側の端部には透析液の排出口６を形成してある。

【００１５】注入側血液ポート３及び排出側血液ポート４は、ケーシング２の両端部にて開口を塞ぐように螺合するもので、ケーシング２と同じくポリカーボネイトにより形成してある。そして、注入側血液ポート３には、血液を注入するための注入口７が突設してあり、排出側血液ポート４には、血液を排出するための排出口８を突設してある。また、注入側血液ポート３とケーシング２との接触部及び排出側血液ポート４とケーシング２との接触部には、それぞれ水密性を保つためのＯリング９，９を配設してある。

【００１６】ケーシング２の内部空間には中空糸束１０を装填してある。即ち、図２（ａ）に示すように、５０００本～１００００本程度の中空糸膜１１…（本実施形態における血液浄化膜に相当）を束ねたものを装填してある。なお、図２（ａ）では、構成を判り易くするため、各中空糸膜１１…を実際のものよりも太く描いてある。

【００１７】ケーシング２における両端の開口部には、ウレタン系樹脂等のシーリング材１２，１２を充填してある。そして、中空糸束１０の端部は、開口した中空糸膜１１…が多数密集していると共に、図２（ｂ）にも示すように、各中空糸膜１１…同士の隙間を水密性を確保した状態でシーリング材１２が塞いでいる。このシーリング材１２，１２は透析液の流入口５及び排出口６を塞いでいない。このため、流入口５，排出口６は、それぞれ、ケーシング２内における中空糸膜１１の外表面側の空間と連通している。従って、中空糸束１０を装填したケーシング２では、血液の流路である中空糸膜１１の内表面１１ａ側と透析液の流路である中空糸膜１１の外表面側とが中空糸膜１１により分離された状態となる。

【００１８】次に、中空糸膜１１について説明する。本実施形態における中空糸膜１１、即ち、血液浄化膜は、ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材とした疎水性高分子膜を中空糸状に紡糸し、尚且つ、その疎水性高分子膜に親水性高分子の一種であるポリビニルピロリドンを付着保持させたものである。

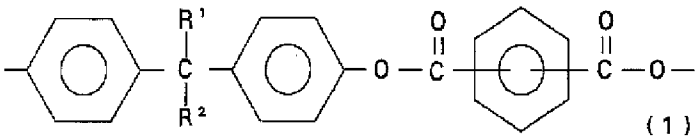
【００１９】そして、このポリビニルピロリドンは、疎水性高分子膜の単位面積当たりの保持量を所定量に調整してある。具体的には、疎水性高分子膜１平方メートルあたりのポリビニルピロリドンの保持量を、３ミリグラム以上５０ミリグラム以下の範囲内としてある。

【００２０】その理由は、ポリビニルピロリドンの保持量を７０ミリグラム以上とした場合には、血液浄化器１からのポリビニルピロリドンの漏出が確認され、また、ポリビニルピロリドンの保持量を１ミリグラム以下とした場合には、凝固した血液成分が中空糸膜１１の内表面１１ａに付着し、この付着した血液成分により比較的短時間で中空糸膜１１の透過能が発揮できなくなってしまうことが確認され、ポリビニルピロリドンの保持量を３ミリグラム以上５０ミリグラム以下の範囲内とすると、ポリビニルピロリドンの漏出や血液成分の付着がなくなることが確認されたからである。

【００２１】また、上記したポリエステル系樹脂は、

【００２２】式

【化１】



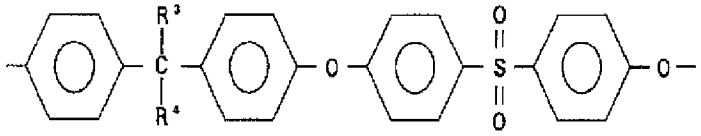
（１）

上記式中、R^1及びR^2は炭素数が１乃至５の低級アルキル基であり、それぞれ同一であっても相違していてもよい。

【００２３】で表される繰り返し単位を有するポリアリレート樹脂であり、ポリスルホン系樹脂は、

【００２４】式

【化２】



（２）

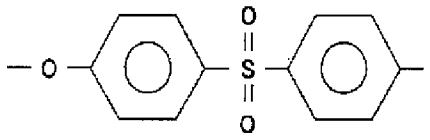
上記式中、R^3及びR^4は炭素数が１乃至５の低級アルキル基であり、

単位が同一であっても相違していてもよい。

【００２５】で表される繰り返し単位及び

【００２６】式

【化３】



（３）

【００２７】で表される繰り返し単位の少なくとも何れかを有するポリスルホン樹脂である。

【００２８】次に、血液浄化膜の作成手順について説明する。なお、本実施形態では、血液浄化器１を製造する過程の中で血液浄化膜が作成されるため、血液浄化器１の製造工程を説明することにする。ここで、図３は、血液浄化器１の製造工程の概略を示すフローチャートである。

【００２９】最初に、疎水性高分子を中空糸膜状に紡糸する（紡糸工程、ステップＳ１）。この紡糸工程では、まず製膜原液の調製を行う。具体的には、ポリエステル系樹脂（Ａ）とポリスルホン系樹脂（Ｂ）との混合重量比（Ａ／Ｂ）を０．１～１０の範囲で定めると共に、両樹脂の合計量（Ａ＋Ｂ）が１０重量%～２５重量%の割合となるように有機溶媒に溶解する。なお、有機溶媒は、ポリエステル系樹脂とポリスルホン系樹脂に対して良溶媒であれば特に制限はないが、Ｎ－メチルピロリドンが最も好適に使用できる。

【００３０】この製膜原液を二重管紡糸口金を用いて芯液とともに凝固液中に吐出し、中空糸状に紡糸する。なお、便宜上、以下の説明では、ポリビニルピロリドン（親水性高分子の一種）が付着保持されていない状態の中空糸膜を、疎水性中空糸膜１１´ということにする。ここで、芯液及び凝固液は、製膜原液を中空糸状に成形するためのものであるが、樹脂溶解に使用した有機溶媒を水に混合した混合溶媒の方が、水単独よりも好ましい。これは、混合溶媒を使用した方が均一なフイブリル構造を形成しやすいためである。なお、混合する有機溶媒としては、樹脂に対する良溶媒であれば特に制限はないが、Ｎ－メチルピロリドンが最も好適に使用できる。

【００３１】このようにして紡糸した疎水性中空糸膜１１´は、その内表面１１ａに緻密層が形成されると共に、この緻密層の外側を覆うように多孔質層が形成される。緻密層は、この膜において、物質の選択透過性並びに透過速度を規定する部分で、５００オングストローム未満の平均孔径を有する孔、具体的には、孔半径３０～１００オングストロームの孔が形成されている。また、多孔質層は緻密層を支持し膜の強度を保つ支持層として機能しており、緻密層よりもかなり粗い孔が形成されている。なお、この疎水性中空糸膜１１´の厚さは、５～７０マイクロメートル程度である。そして、この膜では、分子量１００００００以上の物質は、ほぼ全量（１００%）が透過できない。

【００３２】次に、このように紡糸した疎水性中空糸膜１１´の束ね処理を行う（束ね処理工程、ステップＳ２）。この束ね処理工程では、５０００本～１００００本程度の疎水性中空糸膜１１´を１つの束にするバンドル化がなされる。この疎水性中空糸膜１１´の束（中空糸束１０）は、円筒状のケーシング２の内径に応じた外径に調整してある。

【００３３】次に、中空糸束１０をケーシング２内に装填する（装填工程、ステップＳ３）。この装填工程では、注入側血液ポート３及び排出側血液ポート４が外れた状態のケーシング２内に、中空糸束１０を装填する。このとき、中空糸束１０の外周を予めシートで覆っておき、このシートごとケーシング２内に装填し、装填後にシートを抜き取る。

【００３４】次に、ポッティングを行う（ポッティング工程、ステップＳ４）。このポッティング工程では、ケーシング２の開口部をシーリング材１２により封止（シーリング）するとともに、中空糸束１０におけるケーシング２の外部にはみ出した部分を、ケーシング２の開口部と同一平面２´となるように切断する。この切断により、図２（ａ）で説明した断面が得られる。

【００３５】次に、親水化処理を行う（親水化処理工程、ステップＳ５）。この親水化処理工程では、ケーシング２の両端部に注入側血液ポート３及び排出側血液ポート４を装着（螺着）した後に、注入側血液ポート３の注入口７から所定濃度に調製したポリビニルピロリドンの水溶液（親水性高分子の溶液の一種）を所定流量で注入し、血液浄化器１を通過したポリビニルピロリドンの水溶液を排出側血液ポート４の排出口８から排出する。そして、この処理を数十秒から数十分行い、ポリビニルピロリドンを付着保持させる。

【００３６】即ち、この親水化処理工程では、ポリビニルピロリドンの水溶液を血液浄化器１に接触させることにより、ポリビニルピロリドンを付着保持させている。

なお、この親水化処理工程で用いる親水性高分子の溶液を作製するにあたり、本実施形態では溶媒として精製水を用いたが、精製水以外の液体を溶媒として使用しても構わない。そして、この親水化処理工程を経ることにより、疎水性中空糸膜１１´にはポリビニルピロリドンが付着保持され、本実施形態における血液浄化膜（即ち、中空糸膜１１）が得られる。

【００３７】なお、この親水化処理工程では、親水性高分子溶液の濃度を適宜変えることにより、付着保持させる親水性高分子の量を制御できる。即ち、高濃度の親水性高分子溶液を使用することにより親水性高分子を多く付着保持させることができ、低濃度の親水性高分子溶液を使用することにより少ない量の親水性高分子を付着保持させることができる。

【００３８】例えば、ポリビニルピロリドンの１重量%の水溶液を用いて親水化処理を行うと、ポリアリレート樹脂とポリスルホン樹脂から製造した疎水性高分子膜においては、疎水性高分子膜１平方メートルあたり７０ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜が作製でき、ポリビニルピロリドンの０．０３重量%の水溶液を用いて親水化処理を行うことにより、疎水性高分子膜１平方メートルあたり３ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜が作製できる。また、付着保持されたポリビニルピロリドンの量は、処理前のポリビニルピロリドン水溶液濃度と処理後のポリビニルピロリドン水溶液濃度及び後述する洗浄工程で除去されたポリビニルピロリドンの量（即ち、洗浄液のポリビニルピロリドン濃度）とを比較することで算出できる。

【００３９】また、この親水化処理工程では、親水性高分子の分子量を変えることで膜の厚さ方向の親水化の度合いを変えることができる。即ち、低い分子量の親水性高分子を使用することにより中空糸膜１１の内表面１１ａ側から膜の厚さ方向の全体に亘って親水性高分子を付着保持せしめることができ、高い分子量の親水性高分子を使用することにより中空糸膜１１の内表面１１ａにのみ親水性高分子を付着保持せしめることができる。例えば、ポリビニルピロリドンＫ－３０（平均分子量約４００００）の水溶液を使用して親水化処理を行った場合には、中空糸膜１１の厚さ方向の全体に亘ってポリビニルピロリドンを付着保持せしめることができ、ポリビニルピロリドンＫ－９０（平均分子量約１２０００００）の水溶液を使用して親水化処理行った場合には、中空糸膜１１の内表面１１ａにのみポリビニルピロリドンを付着保持せしめることができる。

【００４０】次に、水洗を行う（洗浄工程、ステップＳ６）。この洗浄工程では、ポリビニルピロリドン（親水性高分子）を付着保持させた血液浄化器１について、余剰な親水性高分子を洗浄液により除去する。具体的には、洗浄液、例えば精製水を血液浄化器１内に流す。この洗浄工程により、血液浄化器１に付着保持している親水性高分子の内、所定の吸着力よりも低い吸着力で吸着している余剰な親水性高分子が洗浄除去される。なお、この洗浄工程後においても血液浄化器１に付着保持されている親水性高分子は、血液浄化器１内を流れる血液によっても離脱しない。また、この洗浄工程で使用する洗浄液は精製水に限定されるものではなく、余剰な親水性高分子を除去できる液体であればよい。

【００４１】そして、洗浄が終了した血液浄化器１に精製水を充填し（ステップＳ７）、この精製水が充填された状態の血液浄化器１に滅菌処理を行う（ステップＳ８）。この滅菌処理工程では、γ線滅菌、蒸気滅菌等を施す。

【００４２】ところで、以上説明した製造工程では、血液浄化器１を製造する過程の中で血液浄化膜（中空糸膜１１）をも製造するようにした例を示したが、紡糸した疎水性高分子膜に対して直接的に親水性高分子の溶液を接触させ、親水性高分子を疎水性高分子膜に付着保持させるようにしてもよい。

【００４３】また、中空糸膜１１から除去可能な開孔剤をポリビニルピロリドン（親水性高分子の一種）と共に製膜原液に添加し、紡糸後に開孔剤を除去することにより、ポリビニルピロリドンの保持量を低く調整することもできる。この方法で製造した血液浄化膜では、膜の厚さ方向の全域に亘って親水性が付与されているが、ポリビニルピロリドンの保持量が低く調整されているので、ポリビニルピロリドンが漏出するのを防止することができる。但し、本実施形態の如く、予め製膜した疎水性高分子膜に親水性高分子の溶液を接触させるようにすると、処理が容易であると共に、親水性高分子の付着量の制御が容易であるという利点を有する。さらに、血液浄化膜を透過できない高い分子量の親水性高分子（例えば、ポリビニルピロリドンＫ－９０）を使用することにより、血液浄化膜における血液接触側の表面にのみ、選択的に親水性高分子を付着保持させることもできる。

【００４４】また、上記した実施形態では中空糸膜１１を例示したが、シート状の膜でもよい。

【００４５】また、上記した実施形態では、血液浄化膜において使用可能な親水性高分子の内、代表的な親水性高分子であるポリビニルピロリドンを例示したが、このポリビニルピロリドンと同様な性質を有する親水性高分子であれば、これに限定されない。但し、本実施形態のようにポリビニルピロリドンを用いた場合には、極く少量で高い血液適合性を発揮し得る血液浄化膜を作製することができる。

【００４６】また、疎水性高分子膜に関し、本実施形態では、ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材とした疎水性高分子膜を例示したが、他の疎水性材料による膜でもよい。但し、本実施形態の如く、ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材

とした疎水性高分子膜を用いた場合には、親水性高分子の溶液を接触させた際に、他の疎水性材料による膜よりも好適に（確実に）親水性高分子を付着保持させられる。

【００４７】

【実施例】次に、本発明の実施例を示して、本発明を更に具体的に説明する。なお、以下の説明では、親水性高分子として血液浄化膜に好適に用いられているポリビニルピロリドンＫ－９０（平均分子量約１２０００００）を用いた場合について説明する。

【００４８】まず、前記式（１）にて示されるポリアリレート樹脂〔（株）ユニチカ製、商品名；Ｕポリマー〕と、前記式（３）にて示されるポリエーテルスルホン樹脂〔住友化学工業（株）製、商品名；スミカエクセルＰＥＳ〕と、Ｎ－メチルピロリドンとから製膜原液を調製した。なお、ポリアリレート樹脂とポリエーテルスルホン樹脂との重量混合比は、１：１とした。また、Ｎ－メチルピロリドン水溶液を凝固液並びに芯液とした。そして、二重管紡糸口金を用いて製膜原液と芯液とを凝固液中へ吐出して疎水性中空糸膜１１´を作製し、この疎水性中空糸膜１１´を１万本程度束ねて中空糸束１０を得た。さらに、この中空糸束１０を円筒状のポリカーボネイト製のケーシング２内に装填した後に、ポリウレタン樹脂をシーリング材１２として用いて端部を接着し、ケーシング２の両端部に血液ポート３，４を接続して、膜面積１．５平方メートルの血液浄化器１を試作した。

【００４９】（実施例１）血液浄化器１にポリビニルピロリドン（ＢＡＳＦ製、商品名；コリドンＫ－９０）の０．１重量%の水溶液を、常温下で、２００ｍＬ／ｍｉｎの流量で約１分間流して親水化処理を行い、疎水性高分子膜１平方メートルあたり１０ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜（中空糸膜１１）を作製した。なお、ポリビニルピロリドンの付着保持量は、親水化処理前におけるポリビニルピロリドン水溶液の濃度と、親水化処理終了時におけるポリビニルピロリドン水溶液の濃度及び洗浄液のポリビニルピロリドン濃度とに基づいて算出した。また、ポリビニルピロリドン水溶液の濃度測定は、Ｍｕｌｌｅｒの方法（Ｋ．Ｍｕｌｌｅｒ，Ｐｈａｍ．Ａｃｔａ，Ｈｅｌｖ．４３（１９６８）１０７－１２２）を用いて行った。

【００５０】そして、この血液浄化膜におけるポリビニルピロリドンの漏出量（溶出量）を調べる試験を行った。具体的には、血液浄化器１を精製水１Ｌで洗浄した後、精製水を血液浄化器１内に充填し、７０℃で３時間加温した後に、充填した液（血液接触部側の液）を抜き取り、ポリビニルピロリドンの濃度を測定した。なお、この試験における血液ポート３，４は、血液浄化膜からの漏出を測定するためポリビニルピロリドンが付着されていないものを用いた。また、この血液浄化膜における限外濾過量（ＵＦＲ、ｍＬ／ｈｒ・ｍｍＨｇ）の経時変化を調べる試験を行った。具体的には、血液浄化器１を精製水１Ｌで洗浄した後、牛血液（ヘマトクリット３０%、総蛋白６．５ｇ／ｄＬ）を２００ｍＬ／ｍｉｎの流量で循環させるとともに濾過流量を９０ｍＬ／ｍｉｎに調整し、限外濾過量の経時変化を測定した。さらに、血液浄化膜の表面（即ち、中空糸膜１１の内表面１１ａ）における血小板の付着状態を観察した。具体的には、限外濾過量の経時変化を調べる試験を行った後の血液浄化膜を、血液浄化器１から切り出すと共に平面状に切り開き、この切り開いた血液浄化膜を乾燥したものを測定サンプルとして、その血液接触面側の表面を電子顕微鏡（ＳＥＭ）で観察した。試験結果及び観察結果を表１並びに図４（限外濾過量の経時変化）に示した。

【００５１】（実施例２）ポリビニルピロリドンの０．５重量%の水溶液を用いて親水化処理（濃度以外の条件は実施例１と同じ、以下同様）を行い、疎水性高分子膜１平方メートルあたり５０ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜を作製した。

【００５２】そして、この血液浄化膜に対しても、ポリビニルピロリドンの漏出量を調べる試験並びに限外濾過量の経時変化を調べる試験を行った（試験内容は、実施例１と同じ）。各試験における試験結果を表１並びに図４に示した。

【００５３】（実施例３）ポリビニルピロリドンの０．０３重量%の水溶液を用いて親水化処理を行い、疎水性高分子膜１平方メートルあたり３ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜を作製した。

【００５４】そして、この血液浄化膜に対しても、ポリビニルピロリドンの漏出量を調べる試験並びに限外濾過量の経時変化を調べる試験を行った（試験内容は、実施例１と同じ）。各試験における試験結果を表１並びに図４に示した。

【００５５】（比較例１）ポリビニルピロリドンの１重量%の水溶液を用いて親水化処理を行い、疎水性高分子膜１平方メートルあたり７０ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜を作製した。

【００５６】そして、この血液浄化膜に対しても、ポリビニルピロリドンの漏出量を調べる試験並びに限外濾過量の経時変化を調べる試験を行った（試験内容は、実施例１と同じ）。各試験における試験結果を表１並びに図４に示した。

【００５７】（比較例２）ポリビニルピロリドンの０．０１重量%の水溶液を用いて親水化処理を行い、疎水性高分子膜１平方メートルあたり１ミリグラムのポリビニルピロリドンが付着保持された血液浄化膜を作製した。

【００５８】そして、この血液浄化膜に対しても、ポリビニルピロリドンの漏出量を調べる試験、限外濾過量の経時変化を調べる試験並びに血小板の付着状態の観察を行った（試験内容は、実施例１と同じ）。各試験における試験結果を表１並びに図４に示した。

【００５９】

【表１】

PVP付着量	PVPの溶出量(mg/l)	牛血UFRの経時変化	血小板付着(SEM)
PVP70mg/m²	5	小さい	−
PVP50mg/m²	N. D.	小さい	−
PVP10mg/m²	N. D.	小さい	付着少ない
PVP3mg/m²	N. D.	小さい	−
PVP1mg/m²	N. D.	大きい	付着多い

【００６０】まず、血液浄化膜における親水性高分子の漏出について検討する。表１に示すように、ポリビニルピロリドンの付着保持量を、疎水性高分子膜１平方メートルあたり７０ミリグラム（付着量７０ミリグラムという、以下同様）とした血液浄化膜（比較例１）では、１リットルあたり５ミリグラムのポリビニルピロリドンの漏出が認められた。一方、付着量５０ミリグラムの血液浄化膜（実施例２）では、ポリビニルピロリドンの漏出は認められなかった（即ち、検出限界以下であった）。同様に、付着量１０，３ミリグラムの血液浄化膜（実施例１，３）でも、ポリビニルピロリドンの漏出は認められなかった。

【００６１】次に、血液浄化膜の透過量の安定性と血液適合性について検討する。図４に示すように、付着量を１ミリグラムとした血液浄化膜（比較例２）では、試験開始直後に約９０ｍＬ／ｈｒ・ｍｍＨｇであった限外濾過量は、時間の経過に伴って急激に低くなり、５０時間経過後には約６０ｍＬ／ｈｒ・ｍｍＨｇであった。さらに、１００時間経過後には約２２ｍＬ／ｈｒ・ｍｍＨｇとなり、それ以後、限外濾過量は徐々に低くなる。そして、２４０時間経過後には、約１７ｍＬ／ｈｒ・ｍｍＨｇとなった。また、血小板の付着状態の観察結果においても、血液浄化膜における血液接触側の表面には、多量の血小板の付着が認められている（表１参照）。従って、親水性高分子の付着量が少なすぎる血液浄化膜では、血液を通じた直後から血液成分が凝固して血液接触側の表面に付着し、膜の劣化が生じる。そして、この劣化は急速に進行し、比較的短期間で使用が困難な状態になることが判る。

【００６２】一方、付着量を３ミリグラムとした血液浄化膜（実施例３）では、試験開始直後に約１０５ｍＬ／ｈｒ・ｍｍＨｇであった限外濾過量は、時間の経過に伴って徐々に低くなり、５０時間経過後には約９３ｍＬ／ｈｒ・ｍｍＨｇであった。それ以後、限外濾過量は緩やかに低くなるが、２４０時間経過後でも、約８５ｍＬ／ｈｒ・ｍｍＨｇの限外濾過量を維持していた。なお、付着量１０，５０ミリグラムの血液浄化膜（実施例１，２）では、試験開始直後から終了までの期間に亘って約１００ｍＬ／ｈｒ・ｍｍＨｇ前後の限外濾過量を維持していた。そして、付着量１０ミリグラムの血液浄化膜（実施例１）では、血液浄化膜における血液接触側の表面には、僅かの血小板の付着しか認められなかった。即ち、1.5mg/l未満（検出限界値未満）N. D. ち、良好な血液適合性を発揮していた。

【００６３】以上から、付着量を３ミリグラム以上にすることにより、血液成分の付着が極めて少なく安定した透過量が得られ、良好な血液適合性を長期間に亘って発揮できることが判る。さらに、付着量を１０ミリグラム以上にすることにより、血液適合性をより一層高める（良好にする）ことができることが判る。

【００６４】そして、上記した親水性高分子の漏出、及び血液適合性を総合すると、付着量１０ミリグラムから５０ミリグラムの血液浄化膜であれば、親水性高分子の漏出阻止と血液適合性をさらに高いレベルで両立させ得ることが判る。

【００６５】なお、親水性高分子の漏出という観点からすれば、親水性高分子の使用量が少ないほど漏出の可能性が少ないので好ましい。従って、付着量１０ミリグラムの血液浄化膜であれば、親水性高分子の漏出阻止と血液適合性とを高いレベルで両立させることができ、尚且つ、漏出阻止を一層確実に行えることが判る。

【００６６】

【発明の効果】以上説明したように、本発明によれば、次の効果を奏する。即ち、請求項１記載の発明によれば、親水性高分子を疎水性高分子膜に保持させた血液浄化膜であって、疎水性高分子膜１平方メートルあたりの親水性高分子の保持量を、３ミリグラム以上５０ミリグラム以下としたので、親水性高分子の漏出阻止と良好な血液適合性とを両立させることができる。

【００６７】請求項２記載の発明によれば、前記親水性高分子がポリビニルピロリドンであるので、極く少量で、良好な血液適合性を発揮し得る血液浄化膜が得られる。

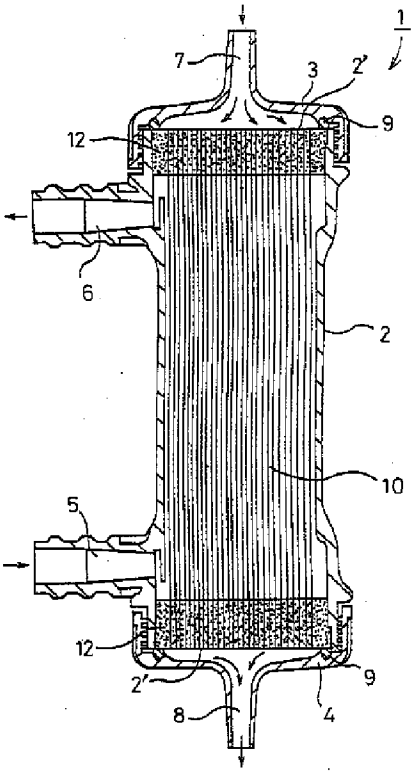
【００６８】請求項３記載の発明によれば、親水性高分子の溶液を疎水性高分子膜に接触させることにより、親水性高分子を疎水性高分子膜に物理的に付着保持せしめたので、付着保持させるための処理が容易であると共に、親水性高分子の付着量の制御を容易に行うことができる。

【００６９】請求項４記載の発明によれば、前記疎水性高分子膜は、ポリアリレート樹脂とポリスルホン樹脂とを主たる膜素材としているので、親水性高分子の溶液を接触させるだけで、親水性高分子を確実に付着保持させることができる。

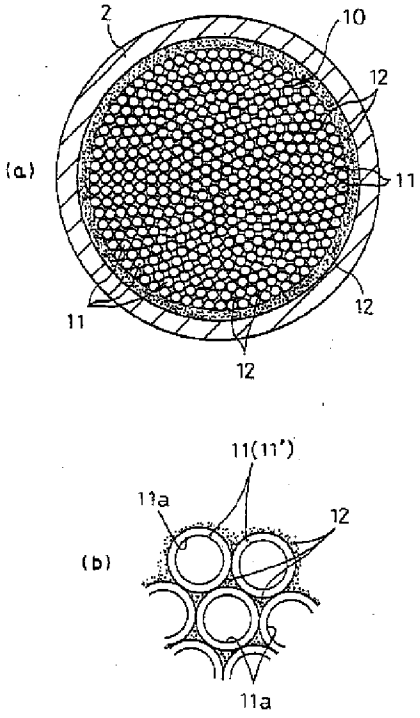
【図面の簡単な説明】

【図１】血液浄化器を断面にした説明図である。
【図２】ケーシングの端部における中空糸束の切断面を示した図で、（ａ）が切断面全体を示した図、（ｂ）が一部を拡大して示した図である。
【図３】血液浄化器の製造工程の概略を示すフローチャートである。
【図４】ポリビニルピロリドンの付着量が異なる血液浄化膜による限外濾過量の経時変化を示した図である。
【符号の説明】
１　血液浄化器
２　ケーシング
３　注入側血液ポート
４　排出側血液ポート
５　透析液の流入口
６　透析液の排出口
７　注入側血液ポートにおける注入口
８　排出側血液ポートにおける排出口
９　Ｏリング
１０　中空糸束
１１　中空糸膜（血液浄化膜）
１１´　疎水性中空糸膜
１１ａ　中空糸膜の内表面
１２　シーリング材

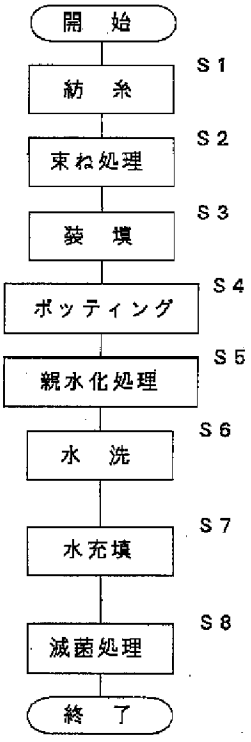
【図１】



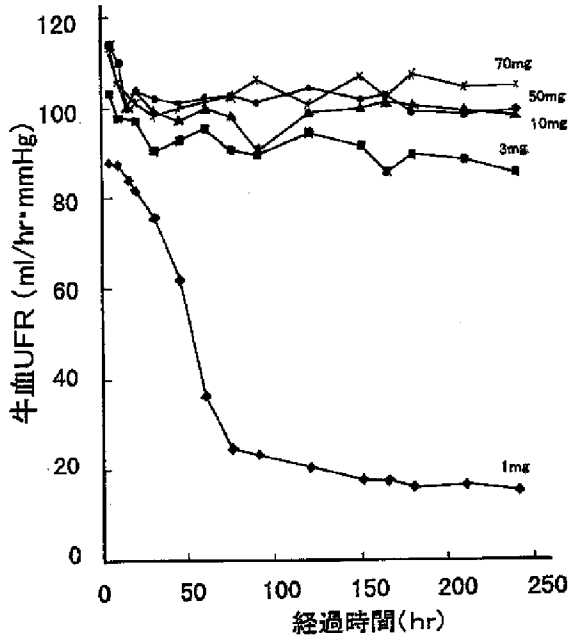
【図２】



【図３】



【図４】



フロントページの続き

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I. PATENT ABSTRACTS OF JAPAN

(11)Publication number : **11-169690**
(43)Date of publication of application : **29.06.1999**

(51)Int.Cl. B01D 69/02
A61M 1/16
B01D 71/40
B01D 71/68

(21)Application number : **09-363136**
(22)Date of filing : **15.12.1997**

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(54) **HEMOCATHERSIS MEMBRANE**

(57)Abstract:
PROBLEM TO BE SOLVED: To make the diapedesis inhibition of a hydrophilic polymer with a hemoeathersis membrane consistent by carrying the polymer on a hydrophobic polymer membrane and the ensure good compatibility with blood by specifying the amt. of the hydrophilic polymer carried on 1 m2 of the membrane.
SOLUTION: A hydrophobic polymer membrane consisting essentially of a polyarylate resin and a polysulfone resin is formed as a hollow fiber membrane by spinning and polyvinylpyrrolidone as a hydrophilic polymer is stuck and carried on the hydrophobic polymer membrane by 3-50 mg/m2 to obtain the objective blood purification membrane. Good compatibility with blood is ensured and the leaching of the hydrophilic polymer is blocked.

LEGAL STATUS
[Date of request for examination] 06.03.2003
[Date of sending the examiner's decision of rejection]
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]
[Date of final disposal for application]
[Patent number] 3688109

[Date of registration]	17.06.2005
[Number of appeal against examiner's decision of rejection]	
[Date of requesting appeal against examiner's decision of rejection]	
[Date of extinction of right]	

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CLAIMS

[Claim(s)]
[Claim 1] Blood purification film which is blood purification film which made the hydrophilic macromolecule hold to a hydrophobic poly membrane, and is characterized by making the amount of maintenance of the hydrophilic macromolecule per 1 square meter of hydrophobic poly membranes into 3mg or more 50mg or less.
[Claim 2] Blood purification film according to claim 1 characterized by said hydrophilic giant molecule being a polyvinyl pyrrolidone.
[Claim 3] Blood purification film according to claim 1 or 2 characterized by carrying out adhesion maintenance of the hydrophilic macromolecule physically to a hydrophobic poly membrane by contacting the solution of a hydrophilic macromolecule to a hydrophobic poly membrane.
[Claim 4] Said hydrophobic poly membrane is blood purification film given in either of claims 1-3 characterized by using polyarylate resin and polysulfone resin as main film raw material.

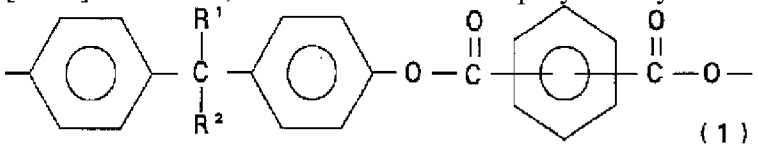
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the blood purification film used for a blood purification therapy.
[0002]
[Description of the Prior Art] A blood purification therapy is the therapy approach of removing the undesired substances in blood (uremia matter etc.). In this blood purification therapy, semipermeable membrane and ultrafiltration membrane are used as blood purification film. For example, the blood purifier which loaded with and constituted in casing the hollow filament bundle which bundled 5000 - about 10000 hollow fibers (what carried out spinning of the blood purification film to the shape of a hollow filament) is used.
[0003] There is a hemodialysis therapy, a hemofiltration therapy, or hemofiltration dialysis in this blood purification therapy. In a hemodialysis therapy, while pouring blood to the internal-surface side of the hollow fiber in blood purifier, dialysing fluid contacts blood and dialysing fluid to an outside-surface side through a sink and a hollow fiber, and diffusion removes the uremia matter and moisture with the superfluous inside of the body. In a hemofiltration therapy, the uremia matter is removed a ** exception by pouring blood to the internal-surface side of the hollow fiber in blood purifier. Moreover, in hemofiltration dialysis, the property of both a

hemofiltration therapy and a hemodialysis therapy, i.e., filtration and diffusion, removes moisture with superfluous uremia matter and inside of the body.
[0004] As blood purification film used by this blood purification therapy, the hydrophilic macromolecule represented by the cellulose and the hydrophobic macromolecule represented by polysulfone and polyester are used suitably. It excels in a mechanical strength and is because there is little effect on a living body. However, generally, in order to use a hydrophobic ingredient (macromolecule) as blood purification film, the hydrophilic property is given to this hydrophobic ingredient in many cases. This is because adhesion of constituents of blood, such as protein and a platelet, tends to take place to the front face of the film manufactured only from the hydrophobic ingredient and lowering of membrane permeability ability in use etc. becomes a problem. That is, by the film manufactured only from the hydrophobic ingredient, it is because good haemocompatibility is difficult to get.
[0005] And generally the approach of adding a hydrophilic macromolecule and producing a film in a film production undiluted solution, from a hydrophobic ingredient as an approach of manufacturing the film with which the hydrophilic property was given, is made. What was using the hydrophilic macromolecule as a puncturing agent can add a hydrophilic property to a hydrophobic ingredient as a result, and this approach can be produced, in order to form membrane structure with a disengageable constituent of blood from a hydrophobic ingredient originally. In this approach, the polyvinyl pyrrolidone is suitably used as a hydrophilic giant molecule added in a film production undiluted solution, for example. That is, a hydrophilic property can be given to a hydrophobic ingredient while a constituent of blood forms disengageable membrane structure proper by adding and carrying out spinning of this polyvinyl pyrrolidone to a film production undiluted solution.
[0006] By this approach, in order to form the membrane structure which can separate a constituent of blood proper, it is necessary to add comparatively a lot of hydrophilic macromolecules. For this reason, on the produced blood purification film, comparatively a lot of hydrophilic macromolecules remain, and processing which prevents a break through of this hydrophilic macromolecule that remained is performed. For example, the hydrophilic macromolecule was made to construct a bridge with heat, a radiation, a chemical, etc., and the break through is prevented.
[0007]
[Problem(s) to be Solved by the Invention] However, even if it performed processing which prevents a break through of a hydrophilic macromolecule since the superfluous hydrophilic macromolecule remained as described above, it was difficult to prevent a break through of a hydrophilic macromolecule certainly. Therefore, there was a possibility that the leaked hydrophilic macromolecule might mix in the inside of the body. And since the hydrophilic macromolecule mixed in the inside of the body may have a certain effect to a living body, it is desirable to remove mixing to the inside of the body of a hydrophilic macromolecule as much as possible.
[0008] this invention is made in view of such a situation, and good haemocompatibility obtains it -- having -- in addition -- and it aims at offering the blood purification film which can also prevent a break through of a hydrophilic macromolecule.
[0009]
[Means for Solving the Problem] In order to attain the above-mentioned object, the thing according to claim 1 in this invention is the blood purification film which made the hydrophilic macromolecule hold to a hydrophobic poly membrane, and is characterized by making the

amount of maintenance of the hydrophilic macromolecule per 1 square meter of hydrophobic poly membranes into 3mg or more 50mg or less.
[0010] Moreover, a thing according to claim 2 is blood purification film which is characterized by said hydrophilic giant molecule being a polyvinyl pyrrolidone in addition to a configuration according to claim 1.
[0011] Moreover, a thing according to claim 3 is blood purification film characterized by carrying out adhesion maintenance of the hydrophilic macromolecule physically to a hydrophobic poly membrane by contacting the solution of a hydrophilic macromolecule to a hydrophobic poly membrane in addition to a configuration according to claim 1 or 2.
[0012] Moreover, a thing according to claim 4 is blood purification film characterized by said hydrophobic poly membrane using polyarylate resin and polysulfone resin as main film raw material in addition to a configuration given in either of claims 1-3.
[0013]
[Embodiment of the Invention] Hereafter, the gestalt of operation of this invention is explained with reference to a drawing. First, the blood purifier using the blood purification film of this invention is explained. Here, drawing 1 is drawing shown by making blood purifier 1 into a cross section, and drawing 2 is drawing having shown the cutting plane of the hollow filament bundle in the edge of casing 2.
[0014] As shown in drawing 1 , blood purifier 1 consists of an impregnation side blood port 3 screwed free [attachment and detachment] to casing 2 and this casing 2, and a blowdown side blood port 4. Casing 2 is the cylindrical member formed of the polycarbonate. And it is the side face of this casing 2, the input 5 of dialysing fluid is formed in the edge by the side of the blowdown side blood port 4, and the exhaust port 6 of dialysing fluid is formed in the edge by the side of the impregnation side blood port 3.
[0015] The impregnation side blood port 3 and the blowdown side blood port 4 are screwed so that opening may be plugged up at the both ends of casing 2, and they are formed by the polycarbonate as well as casing 2. And the inlet 7 for pouring in blood has protruded in the impregnation side blood port 3, and the exhaust port 8 for discharging blood is protruded on the blowdown side blood port 4. Moreover, O rings 9 and 9 for maintaining watertightness, respectively are arranged in the contact section of the impregnation side blood port 3 and casing 2, and the contact section of the blowdown side blood port 4 and casing 2.
[0016] The building envelope of casing 2 is loaded with the hollow filament bundle 10. That is, as shown in drawing 2 (a), it has loaded with what bundled 5000 - about 10000 hollow fiber 11 -- (equivalent to the blood purification film in this operation gestalt). In addition, in drawing 2 (a), in order to make a configuration intelligible, each hollow fiber 11 -- is drawn more thickly than a actual thing.
[0017] Opening of the ends in casing 2 is filled up with the sealing materials 12 and 12, such as urethane system resin. And the edge of the hollow filament bundle 10 is each hollow fiber 11, as it is shown in drawing 2 (b), while it is crowded with much hollow fiber 11 -- which carried out opening. -- Where watertightness is secured, the sealing material 12 has taken up the clearance between comrades. These sealing materials 12 and 12 have not plugged up the input 5 and the exhaust port 6 of dialysing fluid. For this reason, input 5 and an exhaust port 6 are open for free passage with the space by the side of the outside surface of the hollow fiber 11 in casing 2, respectively. Therefore, in the casing 2 which loaded with the hollow filament bundle 10, it will be in the condition that the outside-surface side of the hollow fiber 11 which is the passage of dialysing fluid was separated by the hollow fiber 11 the internal-surface 11a side of the hollow

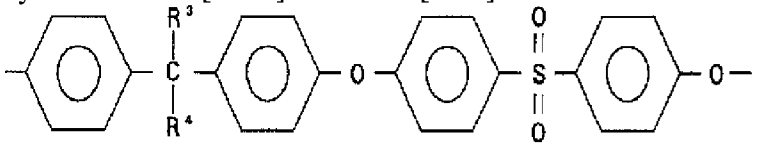
fiber 11 which is the passage of blood.
[0018] Next, a hollow fiber 11 is explained. the hydrophobic poly membrane to which the hollow fiber 11 in this operation gestalt, i.e., the blood purification film, used polyarylate resin and polysulfone resin as main film raw material -- the shape of a hollow filament -- spinning -- carrying out -- in addition -- and the hydrophobic poly membrane is made to carry out adhesion maintenance of the polyvinyl pyrrolidone which is a kind of a hydrophilic giant molecule
[0019] And this polyvinyl pyrrolidone has adjusted the amount of maintenance per unit area of a hydrophobic poly membrane to the specified quantity. Specifically, the amount of maintenance of the polyvinyl pyrrolidone per 1 square meter of hydrophobic poly membranes is made into within the limits of 3mg or more 50mg or less.
[0020] When the amount of maintenance of a polyvinyl pyrrolidone is made into 70mg or more, the reason When a break through of the polyvinyl pyrrolidone from blood purifier 1 is checked and the amount of maintenance of a polyvinyl pyrrolidone is made into 1mg or less The solidified constituent of blood adheres to internal-surface 11a of a hollow fiber 11, and it is checked that it becomes impossible to demonstrate the penetrability of a hollow fiber 11 comparatively by this adhering constituent of blood for a short time. It is because it was checked that a break through of a polyvinyl pyrrolidone and adhesion of a constituent of blood are lost when the amount of maintenance of a polyvinyl pyrrolidone was made into within the limits of 3mg or more 50mg or less.
[0021] Moreover, the above-mentioned polyester system resin is [0022]. Formula [** 1]



(1)

上記式中、R^1及びR^2は炭素数が1乃至5の低級アルキル基であり、
それぞれ同一であっても相違していてもよい。

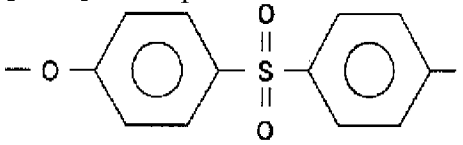
[0023] It is polyarylate resin which comes out and has the repeat unit expressed, and polysulfone system resin is [0024]. Formula [** 2]



(2)

上記式中、R^3及びR^4は炭素数が1乃至5の低級アルキル基であり、
それぞれ同一であっても相違していてもよい。

[0025] The repeat unit come out of and expressed, and [0026] Formula [** 3]



(3)

[0027] It comes out and is polysulfone resin of the repeat unit expressed which has at least any

they are.
[0028] Next, the creation procedure of the blood purification film is explained. In addition, with this operation gestalt, since the blood purification film is created in the process in which blood purifier 1 is manufactured, the production process of blood purifier 1 will be explained. Here, drawing 3 is a flow chart which shows the outline of the production process of blood purifier 1.
[0029] First, spinning of the hydrophobic macromolecule is carried out to the shape of a hollow fiber (a spinning process, step S1). At this spinning process, a film production undiluted solution is prepared first. While defining the mixed weight ratio (A/B) of polyester system resin (A) and polysulfone system resin (B) in 0.1-10, specifically, it dissolves in an organic solvent so that the total quantity (A+B) of both resin may serve as 10 % of the weight - 25% of the weight of a rate. In addition, although there will be especially no limit if an organic solvent is a good solvent to polyester system resin and polysulfone system resin, N-methyl pyrrolidone can use it most suitably.
[0030] Spinning of this film production undiluted solution is carried out to the shape of discharge and a hollow filament into coagulation liquid with core liquid using a double pipe spinneret. In addition, by the following explanation, a polyvinyl pyrrolidone (a kind of a hydrophilic macromolecule) makes for convenience the hollow fiber in the condition that adhesion maintenance is not carried out hydrophobic hollow fiber 11'. Here, although core liquid and coagulation liquid are for fabricating a film production undiluted solution in the shape of a hollow filament, the mixed solvent of a water independent twist which mixed in water the organic solvent used for the resin dissolution is also more desirable. This is for being easy to form fibril structure with more uniform using a mixed solvent. In addition, although there will be especially no limit if it is a good solvent to resin as an organic solvent to mix, N-methyl pyrrolidone can use it most suitably.
[0031] Thus, a porous layer is formed so that hydrophobic hollow fiber 11' which carried out spinning may cover the outside of this compact layer while a compact layer is formed in that internal-surface 11a. A compact layer is the part which specifies a transmission rate in the permselectivity list of the matter in this film, and the hole radius 30-100 A hole is formed in the hole and concrete target which have a less than 500A average aperture. Moreover, the porous layer is functioning as supporters who support a compact layer and maintain membranous reinforcement, and the hole quite coarser than a compact layer is formed. In addition, the thickness of this hydrophobic hollow fiber 11' is about 5-70 micrometers. And by this film, the with a molecular weight of 100000 or more matter cannot penetrate the whole quantity (100%) mostly.
[0032] Next, it processes in the bundle of hydrophobic hollow fiber 11' which carried out spinning in this way (they are down stream processing and step S2 in a bundle). Bundle-ization which makes one bundle 5000 - about 10000 hydrophobic hollow fiber 11' by down stream processing in this bundle is made. The bundle (hollow filament bundle 10) of this hydrophobic hollow fiber 11' is adjusted to the outer diameter according to the bore of the cylinder-like casing 2.
[0033] Next, it loads with the hollow filament bundle 10 into casing 2 (a loading process, step S3). At this loading process, it loads with the hollow filament bundle 10 into the casing 2 in the condition that the impregnation side blood port 3 and the blowdown side blood port 4 separated. At this time, the periphery of the hollow filament bundle 10 is beforehand covered with the sheet, it loads into casing 2 this whole sheet, and a sheet is sampled after loading.
[0034] Next, potting is performed (a potting process, step S4). At this potting process, while

closing opening of casing 2 with a sealing material 12 (sealing), the part overflowing into the exterior of the casing 2 in the hollow filament bundle 10 is cut so that it may become same flat-surface as opening of casing 2 2'. By this cutting, the cross section explained by drawing 2 (a) is obtained.

[0035] Next, hydrophilization processing is performed (hydrophilization down stream processing, step S5). In this hydrophilization down stream processing, after equipping the both ends of casing 2 with the impregnation side blood port 3 and the blowdown side blood port 4 (screwing), the water solution (a kind of the solution of a hydrophilic giant molecule) of a polyvinyl pyrrolidone prepared from the inlet 7 of the impregnation side blood port 3 to predetermined concentration is poured in by the predetermined flow rate, and the water solution of the polyvinyl pyrrolidone which passed blood purifier 1 is discharged from the exhaust port 8 of the blowdown side blood port 4. And this processing is performed from dozens of seconds for dozens minutes, and adhesion maintenance of the polyvinyl pyrrolidone is carried out.

[0036] That is, in this hydrophilization down stream processing, adhesion maintenance of the polyvinyl pyrrolidone is carried out by contacting the water solution of a polyvinyl pyrrolidone to blood purifier 1. In addition, in producing the solution of the hydrophilic macromolecule used by this hydrophilization down stream processing, with this operation gestalt, purified water was used as a solvent, but liquids other than purified water may be used as a solvent. And by passing through this hydrophilization down stream processing, adhesion maintenance of the polyvinyl pyrrolidone is carried out, and the blood purification film (namely, hollow fiber 11) in this operation gestalt is obtained by hydrophobic hollow fiber 11'.

[0037] In addition, the amount of the hydrophilic macromolecule which carries out adhesion maintenance is controllable by this hydrophilization down stream processing by changing the concentration of a hydrophilic polymer solution suitably. That is, by using a hydrophilic high-concentration polymer solution, many adhesion maintenance of the hydrophilic macromolecule can be carried out, and adhesion maintenance of a small quantity of the hydrophilic macromolecule can be carried out by using a low-concentration hydrophilic polymer solution.

[0038] For example, if hydrophilization processing is performed using 1% of the weight of the water solution of a polyvinyl pyrrolidone, in the hydrophobic poly membrane manufactured from polyarylate resin and polysulfone resin, the blood purification film with which adhesion maintenance of the 70mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out can be produced, and the blood purification film with which adhesion maintenance of the 3mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out can be produced by performing hydrophilization processing using 0.03% of the weight of the water solution of a polyvinyl pyrrolidone. Moreover, the amount of the polyvinyl pyrrolidone by which adhesion maintenance was carried out is computable by measuring the amount (namely, polyvinyl-pyrrolidone concentration of a penetrant remover) of the polyvinyl pyrrolidone removed at the polyvinyl-pyrrolidone water-solution concentration before processing, the polyvinyl-pyrrolidone water-solution concentration after processing, and the washing process mentioned later.

[0039] Moreover, in this hydrophilization down stream processing, the degree of the hydrophilization of the membranous thickness direction is changeable by changing the molecular weight of a hydrophilic macromolecule. That is, by using the hydrophilic macromolecule of low molecular weight, it can continue in the membranous whole thickness direction from the internal-surface 11a side of a hollow fiber 11, adhesion maintenance of the hydrophilic macromolecule can be carried out, and only internal-surface 11a of a hollow fiber 11 carries out

adhesion maintenance of the hydrophilic macromolecule by using the hydrophilic macromolecule of high molecular weight. For example, when hydrophilization processing is performed using the water solution of Polyvinylpyrrolidone K30 (average molecular weight 40000 [about]), it can continue in the whole thickness direction of a hollow fiber 11, adhesion maintenance of the polyvinyl pyrrolidone can be carried out, and only internal-surface 11a of a hollow fiber 11 carries out adhesion maintenance of the polyvinyl pyrrolidone at a hydrophilization place Michiyuki **** case using the water solution of Polyvinylpyrrolidone K90 (average molecular weight 1200000 [about]).

[0040] Next, it rinses (a washing process, step S6). At this washing process, a hydrophilic surplus macromolecule is removed by the penetrant remover about the blood purifier 1 which carried out adhesion maintenance of the polyvinyl pyrrolidone (hydrophilic macromolecule). Specifically, a penetrant remover, for example, purified water, is passed in blood purifier 1. Washing clearance of the hydrophilic surplus macromolecule which is sticking to blood purifier 1 according to this washing process by the adsorption power lower than predetermined adsorption power among the hydrophilic macromolecules which are carrying out adhesion maintenance is carried out. In addition, the hydrophilic macromolecule by which adhesion maintenance is carried out after this washing process at blood purifier 1 does not secede from the inside of blood purifier 1 with the flowing blood, either. Moreover, the penetrant remover used at this washing process should just be the liquid from which it is not limited to purified water and a hydrophilic surplus macromolecule can be removed.

[0041] And sterilization processing is performed to the blood purifier 1 in the condition of having filled up with purified water the blood purifier 1 which washing ended (step S7), and having filled up with this purified water (step S8). Gamma ray sterility, wet sterilization, etc. are given in this sterilization down stream processing.

[0042] By the way, although the production process explained above showed the example which also manufactured the blood purification film (hollow fiber 11) in the process in which blood purifier 1 is manufactured, the solution of a hydrophilic macromolecule is directly contacted to the hydrophobic poly membrane which carried out spinning, and you may make it make a hydrophobic poly membrane carry out adhesion maintenance of the hydrophilic macromolecule.

[0043] Moreover, the amount of maintenance of a polyvinyl pyrrolidone can also be low adjusted by adding a puncturing agent removable from a hollow fiber 11 to a film production undiluted solution with a polyvinyl pyrrolidone (a kind of a hydrophilic giant molecule), and removing a puncturing agent after spinning. Although it continues throughout the membranous thickness direction and the hydrophilic property is given by the blood purification film manufactured by this approach, since the amount of maintenance of a polyvinyl pyrrolidone is adjusted low, it can prevent that a polyvinyl pyrrolidone leaks out. However, if it is made to contact the solution of a hydrophilic macromolecule to the hydrophobic poly membrane which produced the film beforehand like this operation gestalt, while processing is easy, it has the advantage that control of the coating weight of a hydrophilic macromolecule is easy. Furthermore, only the front face by the side of the blood contact in the blood purification film can also be made to carry out adhesion maintenance of the hydrophilic giant molecule selectively by using the hydrophilic giant molecule (for example, Polyvinylpyrrolidone K90) of the high molecular weight which cannot penetrate the blood purification film.

[0044] Moreover, the sheet-like film is sufficient although the hollow fiber 11 was illustrated with the above-mentioned operation gestalt.

[0045] Moreover, although the polyvinyl pyrrolidone which is a typical hydrophilic giant

molecule among usable hydrophilic giant molecules was illustrated in the blood purification film with the above-mentioned operation gestalt, if it is the hydrophilic giant molecule which has the same property as this polyvinyl pyrrolidone, it will not be limited to this. However, when a polyvinyl pyrrolidone is used like this operation gestalt, the blood purification film which can demonstrate high haemocompatibility in **** small quantity can be produced.
[0046] Moreover, although the hydrophobic poly membrane which used polyarylate resin and polysulfone resin as main film raw material was illustrated with this operation gestalt about the hydrophobic poly membrane, the film by other hydrophobic ingredients is sufficient. However, when the hydrophobic poly membrane which used polyarylate resin and polysulfone resin as main film raw material like this operation gestalt is used and the solution of a hydrophilic macromolecule is contacted, adhesion maintenance of the hydrophilic macromolecule is carried out more suitably (certainly) than the film by other hydrophobic ingredients.
[0047]
[Example] Next, the example of this invention is shown and this invention is explained still more concretely. In addition, the following explanation explains the case where Polyvinylpyrrolidone K90 (average molecular weight 1200000 [about]) used suitable for the blood purification film as a hydrophilic giant molecule is used.
[0048] First, the film production undiluted solution was prepared from the polyarylate resin [Unitika Make and a trade name;U polymer] shown by said formula (1), the polyether sulphone resin [the Sumitomo Chemical Co., Ltd. make and trade name; SUMIKA Excel PES] shown by said formula (3), and N-methyl pyrrolidone. in addition, the weight of polyarylate resin and polyether sulphone resin -- the mixing ratio was set to 1:1. Moreover, N-methyl pyrrolidone water solution was used as core liquid at the coagulation liquid list. And a film production undiluted solution and core liquid were breathed out into coagulation liquid using the double pipe spinneret, hydrophobic hollow fiber 11' was produced, about 10,000 of this hydrophobic hollow fiber 11' were bundled, and the hollow filament bundle 10 was acquired. Furthermore, after loading with this hollow filament bundle 10 into the casing 2 made from a cylinder-like polycarbonate, polyurethane resin was used as a sealing material 12, the edge was pasted up, the blood ports 3 and 4 were connected to the both ends of casing 2, and the blood purifier 1 of 1.5 square meters of film surface products was made as an experiment.
[0049] (Example 1) 0.1% of the weight of the water solution of a polyvinyl pyrrolidone (the BASF make, a trade name; Kollidon K-90) was poured for about 1 minute by the flow rate of 200 mL/min under ordinary temperature to blood purifier 1, hydrophilization processing was performed, and the blood purification film (hollow fiber 11) with which adhesion maintenance of the 10mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced. In addition, the amount of adhesion maintenance of a polyvinyl pyrrolidone was computed based on the concentration of the polyvinyl-pyrrolidone water solution before hydrophilization processing, and the concentration of the polyvinyl-pyrrolidone water solution at the time of hydrophilization processing termination and the polyvinyl-pyrrolidone concentration of a penetrant remover. Moreover, density measurement of a polyvinyl-pyrrolidone water solution was performed using the approach (KMuller, Pham.Acta, Helv.43 (1968) 107-122) of Muller.
[0050] And the trial which investigates the leak (elution volume) of the polyvinyl pyrrolidone in this blood purification film was performed. After being filled up with purified water after washing blood purifier 1 by purified water 1L in blood purifier 1 and specifically warming it at 70 degrees C for 3 hours, filled liquid (liquid by the side of the blood contact section) was

sampled, and the concentration of a polyvinyl pyrrolidone was measured. In addition, that which does not adhere to the polyvinyl pyrrolidone was used for the blood ports 3 and 4 in this trial in order to measure the break through from the blood purification film. Moreover, the trial which investigates aging of the amount of ultrafiltrations in this blood purification film (UFR, mL/hr-mmHg) was performed. After washing blood purifier 1 by purified water 1L, while circulating bovine blood liquid (hematocrit 30% and total protein 6.5 g/dL) by the flow rate of 200 mL/min, the filtration flow rate was adjusted to 90 mL/min, and, specifically, aging of the amount of ultrafiltrations was measured. Furthermore, the adhesion condition of the platelet in the front face (namely, internal-surface 11a of a hollow fiber 11) of the blood purification film was observed. While cutting down the blood purification film after specifically performing the trial which investigates aging of the amount of ultrafiltrations from blood purifier 1, it was cleared to the plane, and the front face by the side of that blood contact surface was observed with the electron microscope (SEM) by making what dried this cleared blood purification film into a measurement sample. The test result and the observation result were shown in the table 1 list at drawing 4 (aging of the amount of ultrafiltrations).

[0051] (Example 2) hydrophilization processing (conditions other than concentration -- an example 1 -- the same -- the following -- the same) was performed using 0.5% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 50mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0052] And the trial which investigates aging of the amount of ultrafiltrations was performed in the trial list which investigates the leak of a polyvinyl pyrrolidone also to this blood purification film (the content of a trial is the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0053] (Example 3) Hydrophilization processing was performed using 0.03% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 3mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0054] And the trial which investigates aging of the amount of ultrafiltrations was performed in the trial list which investigates the leak of a polyvinyl pyrrolidone also to this blood purification film (the content of a trial is the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0055] (Example 1 of a comparison) Hydrophilization processing was performed using 1% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 70mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0056] And the trial which investigates aging of the amount of ultrafiltrations was performed in the trial list which investigates the leak of a polyvinyl pyrrolidone also to this blood purification film (the content of a trial is the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0057] (Example 2 of a comparison) Hydrophilization processing was performed using 0.01% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 1mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0058] And the adhesion condition of a platelet was observed also to this blood purification film in the trial which investigates the leak of a polyvinyl pyrrolidone, and the trial list which

investigates aging of the amount of ultrafiltrations (the content of a trial is the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0059]

[A table 1]

PVP付着量	PVPの溶出量(mg/l)	牛血UFRの経時変化	血小板付着(SEM)
PVP70mg/m²	5	小さい	−
PVP50mg/m²	N. D.	小さい	−
PVP10mg/m²	N. D.	小さい	付着少ない
PVP3mg/m²	N. D.	小さい	−
PVP1mg/m²	N. D.	大きい	付着多い

N. D. ：1．5mg/l 未満（検出限界値未満）

[0060] First, a break through of the hydrophilic macromolecule in the blood purification film is considered. As shown in a table 1, by the blood purification film (example 1 of a comparison) which made the amount of adhesion maintenance of a polyvinyl pyrrolidone 70mg per 1 square meter of hydrophobic poly membranes (coating weight it is the same as that of the following which it says is 70mg), the break through of a 5mg [per l.] polyvinyl pyrrolidone was accepted. On the other hand, the break through of a polyvinyl pyrrolidone was not accepted by the blood purification film (example 2) with a coating weight of 50mg (that is, it was below limit of detection). Similarly, the break through of a polyvinyl pyrrolidone was not accepted by the blood purification film (examples 1 and 3) with a coating weight of 10 or 3mg, either.

[0061] Next, the stability and haemocompatibility of the amount of transparency of the blood purification film are examined. As shown in drawing 4 , by the blood purification film (example 2 of a comparison) which made coating weight 1mg, the amount of ultrafiltrations which were about 90 mL/hr-mmHg became low rapidly in connection with the passage of time immediately after test initiation, and they were about 60 mL/hr-mmHg after 50-hour progress. Furthermore, after 100-hour progress, it becomes about 22 mL/hr-mmHg, and the amount of ultrafiltrations becomes low gradually after it. And after 240-hour progress, it became about 17 mL/hr-mmHg. Moreover, also in the observation result of the adhesion condition of a platelet, adhesion of a lot of platelets is accepted in the front face by the side of the blood contact in the blood purification film (table 1 reference). Therefore, by the blood purification film which has too little coating weight of a hydrophilic macromolecule, immediately after leading blood, a constituent of blood coagulates from from, it adheres to the front face by the side of blood contact, and degradation of the film arises. And this degradation advances quickly and it turns out that an activity will be in a difficult condition comparatively for a short period of time.

[0062] On the other hand by the blood purification film (example 3) which made coating weight 3mg, the amount of ultrafiltrations which were about 105 mL/hr-mmHg became low gradually in connection with the passage of time immediately after test initiation, and they were about 93 mL/hr-mmHg after 50-hour progress. After it, although the amount of ultrafiltrations became low gently, the amount of ultrafiltrations of about 85 mL/hr-mmHg was maintained also after 240-hour progress. In addition, by the blood purification film (examples 1 and 2) with a coating weight of 10 or 50mg, the amount of ultrafiltrations before and behind about 100 mL/hr-mmHg was maintained for the period from immediately after test initiation to termination. And by the blood purification film (example 1) with a coating weight of 10mg, only adhesion of few platelets was accepted in the front face by the side of the blood contact in the blood purification film. That is, good haemocompatibility was demonstrated.

[0063] As mentioned above, the amount of transparency by which adhesion of a constituent of blood was stabilized very few is obtained, and by making coating weight into 3mg or more shows that it continues and good haemocompatibility can be demonstrated at a long period of time. Furthermore, by making coating weight into 10mg or more shows that haemocompatibility can be raised further (it is made good).
[0064] And putting a break through of the above-mentioned hydrophilic macromolecule and haemocompatibility together, the coating weight of 10mg shows that break-through inhibition and haemocompatibility of a hydrophilic macromolecule may be reconciled on still higher level, if it is the 50mg blood purification film.
[0065] In addition, if it carries out from a viewpoint of a break through of a hydrophilic macromolecule, since there is so little possibility of a break through that there is little amount of the hydrophilic macromolecule used, it is desirable. therefore, compatible [on high level] in break-through inhibition and haemocompatibility of a hydrophilic giant molecule, if it is the blood purification film with a coating weight of 10mg -- it can make -- in addition -- and it turns out that break-through inhibition can much more be ensured.
[0066]
[Effect of the Invention] According to this invention, the following effectiveness is done so as explained above. That is, since according to invention according to claim 1 it is the blood purification film which made the hydrophilic macromolecule hold to a hydrophobic poly membrane and the amount of maintenance of the hydrophilic macromolecule per 1 square meter of hydrophobic poly membranes was made into 3mg or more 50mg or less, break-through inhibition of a hydrophilic macromolecule and good haemocompatibility can be reconciled.
[0067] According to invention according to claim 2, since said hydrophilic giant molecule is a polyvinyl pyrrolidone, the blood purification film which can demonstrate good haemocompatibility in **** small quantity is obtained.
[0068] Since adhesion maintenance of the hydrophilic macromolecule is physically carried out to a hydrophobic poly membrane by contacting the solution of a hydrophilic macromolecule to a hydrophobic poly membrane according to invention according to claim 3, while the processing for carrying out adhesion maintenance is easy, the coating weight of a hydrophilic macromolecule is easily controllable.
[0069] According to invention according to claim 4, since polyarylate resin and polysulfone resin are used as main film raw material, said hydrophobic poly membrane can only contact the solution of a hydrophilic macromolecule, and can carry out adhesion maintenance of the hydrophilic macromolecule certainly.

TECHNICAL FIELD

[Field of the Invention] This invention relates to the blood purification film used for a blood purification therapy.

PRIOR ART

[Description of the Prior Art] A blood purification therapy is the therapy approach of removing the undesired substances in blood (uremia matter etc.). In this blood purification therapy,

semipermeable membrane and ultrafiltration membrane are used as blood purification film. For example, the blood purifier which loaded with and constituted in casing the hollow filament bundle which bundled 5000 - about 10000 hollow fibers (what carried out spinning of the blood purification film to the shape of a hollow filament) is used.

[0003] There is a hemodialysis therapy, a hemofiltration therapy, or hemofiltration dialysis in this blood purification therapy. In a hemodialysis therapy, while pouring blood to the internal-surface side of the hollow fiber in blood purifier, dialysing fluid contacts blood and dialysing fluid to an outside-surface side through a sink and a hollow fiber, and diffusion removes the uremia matter and moisture with the superfluous inside of the body. In a hemofiltration therapy, the uremia matter is removed a ** exception by pouring blood to the internal-surface side of the hollow fiber in blood purifier. Moreover, in hemofiltration dialysis, the property of both a hemofiltration therapy and a hemodialysis therapy, i.e., filtration and diffusion, removes moisture with superfluous uremia matter and inside of the body.

[0004] As blood purification film used by this blood purification therapy, the hydrophilic macromolecule represented by the cellulose and the hydrophobic macromolecule represented by polysulfone and polyester are used suitably. It excels in a mechanical strength and is because there is little effect on a living body. However, generally, in order to use a hydrophobic ingredient (macromolecule) as blood purification film, the hydrophilic property is given to this hydrophobic ingredient in many cases. This is because adhesion of constituents of blood, such as protein and a platelet, tends to take place to the front face of the film manufactured only from the hydrophobic ingredient and lowering of membrane permeability ability in use etc. becomes a problem. That is, by the film manufactured only from the hydrophobic ingredient, it is because good haemocompatibility is difficult to get.

[0005] And generally the approach of adding a hydrophilic macromolecule and producing a film in a film production undiluted solution, from a hydrophobic ingredient as an approach of manufacturing the film with which the hydrophilic property was given, is made. What was using the hydrophilic macromolecule as a puncturing agent can add a hydrophilic property to a hydrophobic ingredient as a result, and this approach can be produced, in order to form membrane structure with a disengageable constituent of blood from a hydrophobic ingredient originally. In this approach, the polyvinyl pyrrolidone is suitably used as a hydrophilic giant molecule added in a film production undiluted solution, for example. That is, a hydrophilic property can be given to a hydrophobic ingredient while a constituent of blood forms disengageable membrane structure proper by adding and carrying out spinning of this polyvinyl pyrrolidone to a film production undiluted solution.

[0006] By this approach, in order to form the membrane structure which can separate a constituent of blood proper, it is necessary to add comparatively a lot of hydrophilic macromolecules. For this reason, on the produced blood purification film, comparatively a lot of hydrophilic macromolecules remain, and processing which prevents a break through of this hydrophilic macromolecule that remained is performed. For example, the hydrophilic macromolecule was made to construct a bridge with heat, a radiation, a chemical, etc., and the break through is prevented.

EFFECT OF THE INVENTION

[Effect of the Invention] According to this invention, the following effectiveness is done so as explained above. That is, since according to invention according to claim 1 it is the blood purification film which made the hydrophilic macromolecule hold to a hydrophobic poly membrane and the amount of maintenance of the hydrophilic macromolecule per 1 square meter of hydrophobic poly membranes was made into 3mg or more 50mg or less, break-through inhibition of a hydrophilic macromolecule and good haemocompatibility can be reconciled.
[0067] According to invention according to claim 2, since said hydrophilic giant molecule is a polyvinyl pyrrolidone, the blood purification film which can demonstrate good haemocompatibility in **** small quantity is obtained.
[0068] Since adhesion maintenance of the hydrophilic macromolecule is physically carried out to a hydrophobic poly membrane by contacting the solution of a hydrophilic macromolecule to a hydrophobic poly membrane according to invention according to claim 3, while the processing for carrying out adhesion maintenance is easy, the coating weight of a hydrophilic macromolecule is easily controllable.
[0069] According to invention according to claim 4, since polyarylate resin and polysulfone resin are used as main film raw material, said hydrophobic poly membrane can only contact the solution of a hydrophilic macromolecule, and can carry out adhesion maintenance of the hydrophilic macromolecule certainly.

TECHNICAL PROBLEM

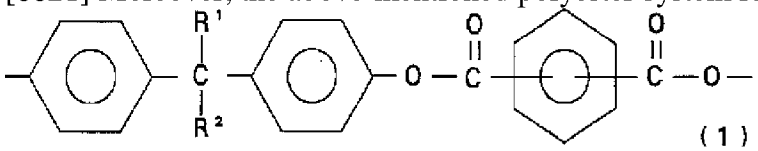
[Problem(s) to be Solved by the Invention] However, even if it performed processing which prevents a break through of a hydrophilic macromolecule since the superfluous hydrophilic macromolecule remained as described above, it was difficult to prevent a break through of a hydrophilic macromolecule certainly. Therefore, there was a possibility that the leaked hydrophilic macromolecule might mix in the inside of the body. And since the hydrophilic macromolecule mixed in the inside of the body may have a certain effect to a living body, it is desirable to remove mixing to the inside of the body of a hydrophilic macromolecule as much as possible.
[0008] this invention is made in view of such a situation, and good haemocompatibility obtains it -- having -- in addition -- and it aims at offering the blood purification film which can also prevent a break through of a hydrophilic macromolecule.

MEANS

[Means for Solving the Problem] In order to attain the above-mentioned object, the thing according to claim 1 in this invention is the blood purification film which made the hydrophilic macromolecule hold to a hydrophobic poly membrane, and is characterized by making the amount of maintenance of the hydrophilic macromolecule per 1 square meter of hydrophobic poly membranes into 3mg or more 50mg or less.
[0010] Moreover, a thing according to claim 2 is blood purification film which is characterized by said hydrophilic giant molecule being a polyvinyl pyrrolidone in addition to a configuration according to claim 1.
[0011] Moreover, a thing according to claim 3 is blood purification film characterized by

carrying out adhesion maintenance of the hydrophilic macromolecule physically to a hydrophobic poly membrane by contacting the solution of a hydrophilic macromolecule to a hydrophobic poly membrane in addition to a configuration according to claim 1 or 2.
[0012] Moreover, a thing according to claim 4 is blood purification film characterized by said hydrophobic poly membrane using polyarylate resin and polysulfone resin as main film raw material in addition to a configuration given in either of claims 1-3.
[0013]
[Embodiment of the Invention] Hereafter, the gestalt of operation of this invention is explained with reference to a drawing. First, the blood purifier using the blood purification film of this invention is explained. Here, drawing 1 is drawing shown by making blood purifier 1 into a cross section, and drawing 2 is drawing having shown the cutting plane of the hollow filament bundle in the edge of casing 2.
[0014] As shown in drawing 1 , blood purifier 1 consists of an impregnation side blood port 3 screwed free [attachment and detachment] to casing 2 and this casing 2, and a blowdown side blood port 4. Casing 2 is the cylindrical member formed of the polycarbonate. And it is the side face of this casing 2, the input 5 of dialysing fluid is formed in the edge by the side of the blowdown side blood port 4, and the exhaust port 6 of dialysing fluid is formed in the edge by the side of the impregnation side blood port 3.
[0015] The impregnation side blood port 3 and the blowdown side blood port 4 are screwed so that opening may be plugged up at the both ends of casing 2, and they are formed by the polycarbonate as well as casing 2. And the inlet 7 for pouring in blood has protruded in the impregnation side blood port 3, and the exhaust port 8 for discharging blood is protruded on the blowdown side blood port 4. Moreover, O rings 9 and 9 for maintaining watertightness, respectively are arranged in the contact section of the impregnation side blood port 3 and casing 2, and the contact section of the blowdown side blood port 4 and casing 2.
[0016] The building envelope of casing 2 is loaded with the hollow filament bundle 10. That is, as shown in drawing 2 (a), it has loaded with what bundled 5000 - about 10000 hollow fiber 11 -- (equivalent to the blood purification film in this operation gestalt). In addition, in drawing 2 (a), in order to make a configuration intelligible, each hollow fiber 11 -- is drawn more thickly than a actual thing.
[0017] Opening of the ends in casing 2 is filled up with the sealing materials 12 and 12, such as urethane system resin. And the edge of the hollow filament bundle 10 is each hollow fiber 11, as it is shown in drawing 2 (b), while it is crowded with much hollow fiber 11 -- which carried out opening. -- Where watertightness is secured, the sealing material 12 has taken up the clearance between comrades. These sealing materials 12 and 12 have not plugged up the input 5 and the exhaust port 6 of dialysing fluid. For this reason, input 5 and an exhaust port 6 are open for free passage with the space by the side of the outside surface of the hollow fiber 11 in casing 2, respectively. Therefore, in the casing 2 which loaded with the hollow filament bundle 10, it will be in the condition that the outside-surface side of the hollow fiber 11 which is the passage of dialysing fluid was separated by the hollow fiber 11 the internal-surface 11a side of the hollow fiber 11 which is the passage of blood.
[0018] Next, a hollow fiber 11 is explained. the hydrophobic poly membrane to which the hollow fiber 11 in this operation gestalt, i.e., the blood purification film, used polyarylate resin and polysulfone resin as main film raw material -- the shape of a hollow filament -- spinning -- carrying out -- in addition -- and the hydrophobic poly membrane is made to carry out adhesion maintenance of the polyvinyl pyrrolidone which is a kind of a hydrophilic giant molecule

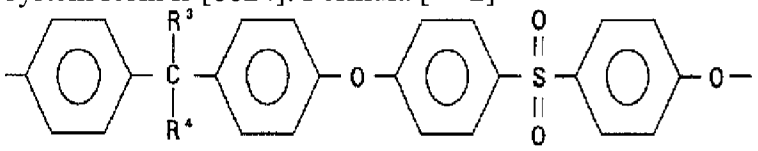
[0019] And this polyvinyl pyrrolidone has adjusted the amount of maintenance per unit area of a hydrophobic poly membrane to the specified quantity. Specifically, the amount of maintenance of the polyvinyl pyrrolidone per 1 square meter of hydrophobic poly membranes is made into within the limits of 3mg or more 50mg or less.
[0020] When the amount of maintenance of a polyvinyl pyrrolidone is made into 70mg or more, the reason When a break through of the polyvinyl pyrrolidone from blood purifier 1 is checked and the amount of maintenance of a polyvinyl pyrrolidone is made into 1mg or less The solidified constituent of blood adheres to internal-surface 11a of a hollow fiber 11, and it is checked that it becomes impossible to demonstrate the penetrability of a hollow fiber 11 comparatively by this adhering constituent of blood for a short time. It is because it was checked that a break through of a polyvinyl pyrrolidone and adhesion of a constituent of blood are lost when the amount of maintenance of a polyvinyl pyrrolidone was made into within the limits of 3mg or more 50mg or less.
[0021] Moreover, the above-mentioned polyester system resin is [0022]. Formula [** 1]



(1)

上記式中、R^1及びR^2は炭素数が1乃至5の低級アルキル基であり、
それぞれ同一であっても相違していてもよい。

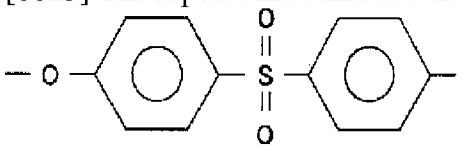
[0023] It is polyarylate resin which comes out and has the repeat unit expressed, and polysulfone system resin is [0024]. Formula [** 2]



(2)

上記式中、R^3及びR^4は炭素数が1乃至5の低級アルキル基であり、
それぞれ同一であっても相違していてもよい。

[0025] The repeat unit come out of and expressed, and [0026] Formula [** 3]



(3)

[0027] It comes out and is polysulfone resin of the repeat unit expressed which has at least any they are.
[0028] Next, the creation procedure of the blood purification film is explained. In addition, with this operation gestalt, since the blood purification film is created in the process in which blood purifier 1 is manufactured, the production process of blood purifier 1 will be explained. Here, drawing 3 is a flow chart which shows the outline of the production process of blood purifier 1.
[0029] First, spinning of the hydrophobic macromolecule is carried out to the shape of a hollow

fiber (a spinning process, step S1). At this spinning process, a film production undiluted solution is prepared first. While defining the mixed weight ratio (A/B) of polyester system resin (A) and polysulfone system resin (B) in 0.1-10, specifically, it dissolves in an organic solvent so that the total quantity (A+B) of both resin may serve as 10 % of the weight - 25% of the weight of a rate. In addition, although there will be especially no limit if an organic solvent is a good solvent to polyester system resin and polysulfone system resin, N-methyl pyrrolidone can use it most suitably.

[0030] Spinning of this film production undiluted solution is carried out to the shape of discharge and a hollow filament into coagulation liquid with core liquid using a double pipe spinneret. In addition, by the following explanation, a polyvinyl pyrrolidone (a kind of a hydrophilic macromolecule) makes for convenience the hollow fiber in the condition that adhesion maintenance is not carried out hydrophobic hollow fiber 11'. Here, although core liquid and coagulation liquid are for fabricating a film production undiluted solution in the shape of a hollow filament, the mixed solvent of a water independent twist which mixed in water the organic solvent used for the resin dissolution is also more desirable. This is for being easy to form fibril structure with more uniform using a mixed solvent. In addition, although there will be especially no limit if it is a good solvent to resin as an organic solvent to mix, N-methyl pyrrolidone can use it most suitably.

[0031] Thus, a porous layer is formed so that hydrophobic hollow fiber 11' which carried out spinning may cover the outside of this compact layer while a compact layer is formed in that internal-surface 11a. A compact layer is the part which specifies a transmission rate in the permselectivity list of the matter in this film, and the hole radius 30-100 A hole is formed in the hole and concrete target which have a less than 500A average aperture. Moreover, the porous layer is functioning as supporters who support a compact layer and maintain membranous reinforcement, and the hole quite coarser than a compact layer is formed. In addition, the thickness of this hydrophobic hollow fiber 11' is about 5-70 micrometers. And by this film, the with a molecular weight of 100000 or more matter cannot penetrate the whole quantity (100%) mostly.

[0032] Next, it processes in the bundle of hydrophobic hollow fiber 11' which carried out spinning in this way (they are down stream processing and step S2 in a bundle). Bundle-ization which makes one bundle 5000 - about 10000 hydrophobic hollow fiber 11' by down stream processing in this bundle is made. The bundle (hollow filament bundle 10) of this hydrophobic hollow fiber 11' is adjusted to the outer diameter according to the bore of the cylinder-like casing 2.

[0033] Next, it loads with the hollow filament bundle 10 into casing 2 (a loading process, step S3). At this loading process, it loads with the hollow filament bundle 10 into the casing 2 in the condition that the impregnation side blood port 3 and the blowdown side blood port 4 separated. At this time, the periphery of the hollow filament bundle 10 is beforehand covered with the sheet, it loads into casing 2 this whole sheet, and a sheet is sampled after loading.

[0034] Next, potting is performed (a potting process, step S4). At this potting process, while closing opening of casing 2 with a sealing material 12 (sealing), the part overflowing into the exterior of the casing 2 in the hollow filament bundle 10 is cut so that it may become same flat-surface as opening of casing 2 2'. By this cutting, the cross section explained by drawing 2 (a) is obtained.

[0035] Next, hydrophilization processing is performed (hydrophilization down stream processing, step S5). In this hydrophilization down stream processing, after equipping the both

ends of casing 2 with the impregnation side blood port 3 and the blowdown side blood port 4 (screwing), the water solution (a kind of the solution of a hydrophilic giant molecule) of a polyvinyl pyrrolidone prepared from the inlet 7 of the impregnation side blood port 3 to predetermined concentration is poured in by the predetermined flow rate, and the water solution of the polyvinyl pyrrolidone which passed blood purifier 1 is discharged from the exhaust port 8 of the blowdown side blood port 4. And this processing is performed from dozens of seconds for dozens minutes, and adhesion maintenance of the polyvinyl pyrrolidone is carried out.

[0036] That is, in this hydrophilization down stream processing, adhesion maintenance of the polyvinyl pyrrolidone is carried out by contacting the water solution of a polyvinyl pyrrolidone to blood purifier 1. In addition, in producing the solution of the hydrophilic macromolecule used by this hydrophilization down stream processing, with this operation gestalt, purified water was used as a solvent, but liquids other than purified water may be used as a solvent. And by passing through this hydrophilization down stream processing, adhesion maintenance of the polyvinyl pyrrolidone is carried out, and the blood purification film (namely, hollow fiber 11) in this operation gestalt is obtained by hydrophobic hollow fiber 11'.

[0037] In addition, the amount of the hydrophilic macromolecule which carries out adhesion maintenance is controllable by this hydrophilization down stream processing by changing the concentration of a hydrophilic polymer solution suitably. That is, by using a hydrophilic high-concentration polymer solution, many adhesion maintenance of the hydrophilic macromolecule can be carried out, and adhesion maintenance of a small quantity of the hydrophilic macromolecule can be carried out by using a low-concentration hydrophilic polymer solution.

[0038] For example, if hydrophilization processing is performed using 1% of the weight of the water solution of a polyvinyl pyrrolidone, in the hydrophobic poly membrane manufactured from polyarylate resin and polysulfone resin, the blood purification film with which adhesion maintenance of the 70mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out can be produced, and the blood purification film with which adhesion maintenance of the 3mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out can be produced by performing hydrophilization processing using 0.03% of the weight of the water solution of a polyvinyl pyrrolidone. Moreover, the amount of the polyvinyl pyrrolidone by which adhesion maintenance was carried out is computable by measuring the amount (namely, polyvinyl-pyrrolidone concentration of a penetrant remover) of the polyvinyl pyrrolidone removed at the polyvinyl-pyrrolidone water-solution concentration before processing, the polyvinyl-pyrrolidone water-solution concentration after processing, and the washing process mentioned later.

[0039] Moreover, in this hydrophilization down stream processing, the degree of the hydrophilization of the membranous thickness direction is changeable by changing the molecular weight of a hydrophilic macromolecule. That is, by using the hydrophilic macromolecule of low molecular weight, it can continue in the membranous whole thickness direction from the internal-surface 11a side of a hollow fiber 11, adhesion maintenance of the hydrophilic macromolecule can be carried out, and only internal-surface 11a of a hollow fiber 11 carries out adhesion maintenance of the hydrophilic macromolecule by using the hydrophilic macromolecule of high molecular weight. For example, when hydrophilization processing is performed using the water solution of Polyvinylpyrrolidone K30 (average molecular weight 40000 [about]), it can continue in the whole thickness direction of a hollow fiber 11, adhesion maintenance of the polyvinyl pyrrolidone can be carried out, and only internal-surface 11a of a hollow fiber 11 carries out adhesion maintenance of the polyvinyl pyrrolidone at a

hydrophilization place Michiyuki **** case using the water solution of Polyvinylpyrrolidone K90 (average molecular weight 1200000 [about]).
[0040] Next, it rinses (a washing process, step S6). At this washing process, a hydrophilic surplus macromolecule is removed by the penetrant remover about the blood purifier 1 which carried out adhesion maintenance of the polyvinyl pyrrolidone (hydrophilic macromolecule). Specifically, a penetrant remover, for example, purified water, is passed in blood purifier 1. Washing clearance of the hydrophilic surplus macromolecule which is sticking to blood purifier 1 according to this washing process by the adsorption power lower than predetermined adsorption power among the hydrophilic macromolecules which are carrying out adhesion maintenance is carried out. In addition, the hydrophilic macromolecule by which adhesion maintenance is carried out after this washing process at blood purifier 1 does not secede from the inside of blood purifier 1 with the flowing blood, either. Moreover, the penetrant remover used at this washing process should just be the liquid from which it is not limited to purified water and a hydrophilic surplus macromolecule can be removed.
[0041] And sterilization processing is performed to the blood purifier 1 in the condition of having filled up with purified water the blood purifier 1 which washing ended (step S7), and having filled up with this purified water (step S8). Gamma ray sterility, wet sterilization, etc. are given in this sterilization down stream processing.
[0042] By the way, although the production process explained above showed the example which also manufactured the blood purification film (hollow fiber 11) in the process in which blood purifier 1 is manufactured, the solution of a hydrophilic macromolecule is directly contacted to the hydrophobic poly membrane which carried out spinning, and you may make it make a hydrophobic poly membrane carry out adhesion maintenance of the hydrophilic macromolecule.
[0043] Moreover, the amount of maintenance of a polyvinyl pyrrolidone can also be low adjusted by adding a puncturing agent removable from a hollow fiber 11 to a film production undiluted solution with a polyvinyl pyrrolidone (a kind of a hydrophilic giant molecule), and removing a puncturing agent after spinning. Although it continues throughout the membranous thickness direction and the hydrophilic property is given by the blood purification film manufactured by this approach, since the amount of maintenance of a polyvinyl pyrrolidone is adjusted low, it can prevent that a polyvinyl pyrrolidone leaks out. However, if it is made to contact the solution of a hydrophilic macromolecule to the hydrophobic poly membrane which produced the film beforehand like this operation gestalt, while processing is easy, it has the advantage that control of the coating weight of a hydrophilic macromolecule is easy. Furthermore, only the front face by the side of the blood contact in the blood purification film can also be made to carry out adhesion maintenance of the hydrophilic giant molecule selectively by using the hydrophilic giant molecule (for example, Polyvinylpyrrolidone K90) of the high molecular weight which cannot penetrate the blood purification film.
[0044] Moreover, the sheet-like film is sufficient although the hollow fiber 11 was illustrated with the above-mentioned operation gestalt.
[0045] Moreover, although the polyvinyl pyrrolidone which is a typical hydrophilic giant molecule among usable hydrophilic giant molecules was illustrated in the blood purification film with the above-mentioned operation gestalt, if it is the hydrophilic giant molecule which has the same property as this polyvinyl pyrrolidone, it will not be limited to this. However, when a polyvinyl pyrrolidone is used like this operation gestalt, the blood purification film which can demonstrate high haemocompatibility in **** small quantity can be produced.
[0046] Moreover, although the hydrophobic poly membrane which used polyarylate resin and

polysulfone resin as main film raw material was illustrated with this operation gestalt about the hydrophobic poly membrane, the film by other hydrophobic ingredients is sufficient. However, when the hydrophobic poly membrane which used polyarylate resin and polysulfone resin as main film raw material like this operation gestalt is used and the solution of a hydrophilic macromolecule is contacted, adhesion maintenance of the hydrophilic macromolecule is carried out more suitably (certainly) than the film by other hydrophobic ingredients.

EXAMPLE

[Example] Next, the example of this invention is shown and this invention is explained still more concretely. In addition, the following explanation explains the case where Polyvinylpyrrolidone K90 (average molecular weight 1200000 [about]) used suitable for the blood purification film as a hydrophilic giant molecule is used.

[0048] First, the film production undiluted solution was prepared from the polyarylate resin [Unitika Make and a trade name;U polymer] shown by said formula (1), the polyether sulphone resin [the Sumitomo Chemical Co., Ltd. make and trade name; SUMIKA Excel PES] shown by said formula (3), and N-methyl pyrrolidone. in addition, the weight of polyarylate resin and polyether sulphone resin -- the mixing ratio was set to 1:1. Moreover, N-methyl pyrrolidone water solution was used as core liquid at the coagulation liquid list. And a film production undiluted solution and core liquid were breathed out into coagulation liquid using the double pipe spinneret, hydrophobic hollow fiber 11' was produced, about 10,000 of this hydrophobic hollow fiber 11' were bundled, and the hollow filament bundle 10 was acquired. Furthermore, after loading with this hollow filament bundle 10 into the casing 2 made from a cylinder-like polycarbonate, polyurethane resin was used as a sealing material 12, the edge was pasted up, the blood ports 3 and 4 were connected to the both ends of casing 2, and the blood purifier 1 of 1.5 square meters of film surface products was made as an experiment.

[0049] (Example 1) 0.1% of the weight of the water solution of a polyvinyl pyrrolidone (the BASF make, a trade name; Kollidon K-90) was poured for about 1 minute by the flow rate of 200 mL/min under ordinary temperature to blood purifier 1, hydrophilization processing was performed, and the blood purification film (hollow fiber 11) with which adhesion maintenance of the 10mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced. In addition, the amount of adhesion maintenance of a polyvinyl pyrrolidone was computed based on the concentration of the polyvinyl-pyrrolidone water solution before hydrophilization processing, and the concentration of the polyvinyl-pyrrolidone water solution at the time of hydrophilization processing termination and the polyvinyl-pyrrolidone concentration of a penetrant remover. Moreover, density measurement of a polyvinyl-pyrrolidone water solution was performed using the approach (KMuller, Pham.Acta, Helv.43 (1968) 107-122) of Muller.

[0050] And the trial which investigates the leak (elution volume) of the polyvinyl pyrrolidone in this blood purification film was performed. After being filled up with purified water after washing blood purifier 1 by purified water 1L in blood purifier 1 and specifically warming it at 70 degrees C for 3 hours, filled liquid (liquid by the side of the blood contact section) was sampled, and the concentration of a polyvinyl pyrrolidone was measured. In addition, that which does not adhere to the polyvinyl pyrrolidone was used for the blood ports 3 and 4 in this trial in order to measure the exsorption from the blood purification film. Moreover, the trial which

investigates aging of the amount of ultrafiltrations in this blood purification film (UFR, mL/hr-mmHg) was performed. After washing blood purifier 1 by purified water 1L, while circulating bovine blood liquid (hematocrit 30% and total protein 6.5 g/dL) by the flow rate of 200 mL/min, the filtration flow rate was adjusted to 90 mL/min, and, specifically, aging of the amount of ultrafiltrations was measured. Furthermore, the adhesion condition of the platelet in the front face (namely, internal-surface 11a of a hollow fiber 11) of the blood purification film was observed. While cutting down the blood purification film after specifically performing the trial which investigates aging of the amount of ultrafiltrations from blood purifier 1, it was cleared to the plane, and the front face by the side of that blood contact surface was observed with the electron microscope (SEM) by making what dried this cleared blood purification film into a measurement sample. The test result and the observation result were shown in the table 1 list at drawing 4 (aging of the amount of ultrafiltrations).

[0051] (Example 2) hydrophilization processing (conditions other than concentration -- an example 1 -- the same -- the following -- the same) was performed using 0.5% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 50mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0052] And the trial which investigates aging of the amount of ultrafiltrations was performed in the trial list which investigates the leak of a polyvinyl pyrrolidone also to this blood purification film (the contents of a trial are the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0053] (Example 3) Hydrophilization processing was performed using 0.03% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 3mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0054] And the trial which investigates aging of the amount of ultrafiltrations was performed in the trial list which investigates the leak of a polyvinyl pyrrolidone also to this blood purification film (the contents of a trial are the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0055] (Example 1 of a comparison) Hydrophilization processing was performed using 1% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 70mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0056] And the trial which investigates aging of the amount of ultrafiltrations was performed in the trial list which investigates the leak of a polyvinyl pyrrolidone also to this blood purification film (the contents of a trial are the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0057] (Example 2 of a comparison) Hydrophilization processing was performed using 0.01% of the weight of the water solution of a polyvinyl pyrrolidone, and the blood purification film with which adhesion maintenance of the 1mg [per 1 square meter of hydrophobic poly membranes] polyvinyl pyrrolidone was carried out was produced.

[0058] And the adhesion condition of a platelet was observed also to this blood purification film in the trial which investigates the leak of a polyvinyl pyrrolidone, and the trial list which investigates aging of the amount of ultrafiltrations (the contents of a trial are the same as an example 1). The test result in each trial was shown in the table 1 list at drawing 4 .

[0059]

[Table 1]

PVP付着量	PVPの溶出量(mg/l)	牛血UFRの経時変化	血小板付着(SEM)
PVP70mg/m²	5	小さい	−
PVP50mg/m²	N. D.	小さい	−
PVP10mg/m²	N. D.	小さい	付着少ない
PVP3mg/m²	N. D.	小さい	−
PVP1mg/m²	N. D.	大きい	付着多い

N．D．：1．5mg/l 未満（検出限界値未満）

[0060] First, exsorption of the hydrophilic macromolecule in the blood purification film is considered. As shown in Table 1, by the blood purification film (example 1 of a comparison) which made the amount of adhesion maintenance of a polyvinyl pyrrolidone 70mg per 1 square meter of hydrophobic poly membranes (coating weight it is the same as that of the following which it says is 70mg), exsorption of a 5mg [per l.] polyvinyl pyrrolidone was accepted. On the other hand, exsorption of a polyvinyl pyrrolidone was not accepted by the blood purification film (example 2) with a coating weight of 50mg (that is, it was below limit of detection). Similarly, exsorption of a polyvinyl pyrrolidone was not accepted by the blood purification film (examples 1 and 3) with a coating weight of 10 or 3mg, either.

[0061] Next, the stability and haemocompatibility of the amount of transparency of the blood purification film are examined. As shown in drawing 4 , by the blood purification film (example 2 of a comparison) which made coating weight 1mg, the amount of ultrafiltrations which were about 90 mL/hr-mmHg became low rapidly in connection with the passage of time immediately after test initiation, and they were about 60 mL/hr-mmHg after 50-hour progress. Furthermore, after 100-hour progress, it becomes about 22 mL/hr-mmHg and the amount of ultrafiltrations becomes low gradually after it. And after 240-hour progress, it became about 17 mL/hr-mmHg. Moreover, also in the observation result of the adhesion condition of a platelet, adhesion of a lot of platelets is accepted in the front face by the side of the blood contact in the blood purification film (refer to Table 1). Therefore, by the blood purification film which has too little coating weight of a hydrophilic macromolecule, immediately after leading blood, a constituent of blood coagulates from from, it adheres to the front face by the side of blood contact, and degradation of the film arises. And this degradation advances quickly and it turns out that use will be in a difficult condition comparatively for a short period of time.

[0062] On the other hand by the blood purification film (example 3) which made coating weight 3mg, the amount of ultrafiltrations which were about 105 mL/hr-mmHg became low gradually in connection with the passage of time immediately after test initiation, and they were about 93 mL/hr-mmHg after 50-hour progress. After it, although the amount of ultrafiltrations became low gently, the amount of ultrafiltrations of about 85 mL/hr-mmHg was maintained also after 240-hour progress. In addition, by the blood purification film (examples 1 and 2) with a coating weight of 10 or 50mg, the amount of ultrafiltrations before and behind about 100 mL/hr-mmHg was maintained for the period from immediately after test initiation to termination. And by the blood purification film (example 1) with a coating weight of 10mg, only adhesion of few platelets was accepted in the front face by the side of the blood contact in the blood purification film. That is, good haemocompatibility was demonstrated.

[0063] As mentioned above, the amount of transparency by which adhesion of a constituent of blood was stabilized very few is obtained, and by making coating weight into 3mg or more shows that it continues and good haemocompatibility can be demonstrated at a long period of

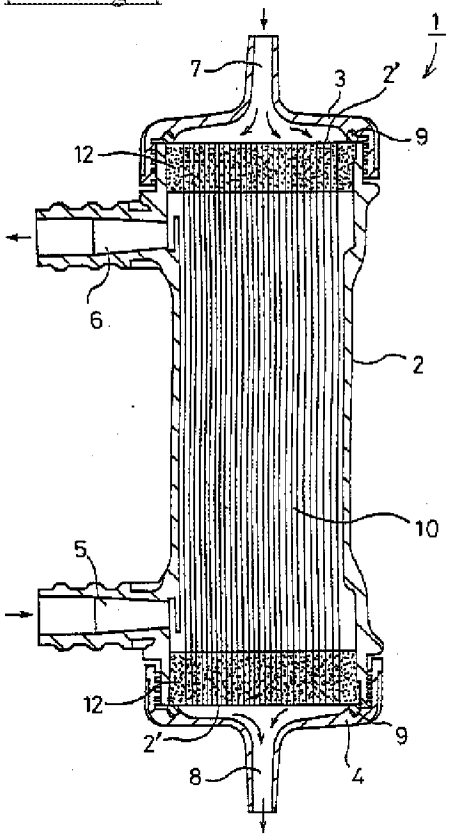
time. Furthermore, by making coating weight into 10mg or more shows that haemocompatibility can be raised further (it is made good).
[0064] And putting exsorption of the above-mentioned hydrophilic macromolecule and haemocompatibility together, the coating weight of 10mg shows that exsorption inhibition and haemocompatibility of a hydrophilic macromolecule may be reconciled on still higher level, if it is the 50mg blood purification film.
[0065] In addition, if it carries out from a viewpoint of exsorption of a hydrophilic macromolecule, since there is so little possibility of exsorption that there is little amount of the hydrophilic macromolecule used, it is desirable. therefore, compatible [on high level] in exsorption inhibition and haemocompatibility of a hydrophilic giant molecule, if it is the blood purification film with a coating weight of 10mg -- it can make -- in addition -- and it turns out that exsorption inhibition can much more be ensured.

DESCRIPTION OF DRAWINGS

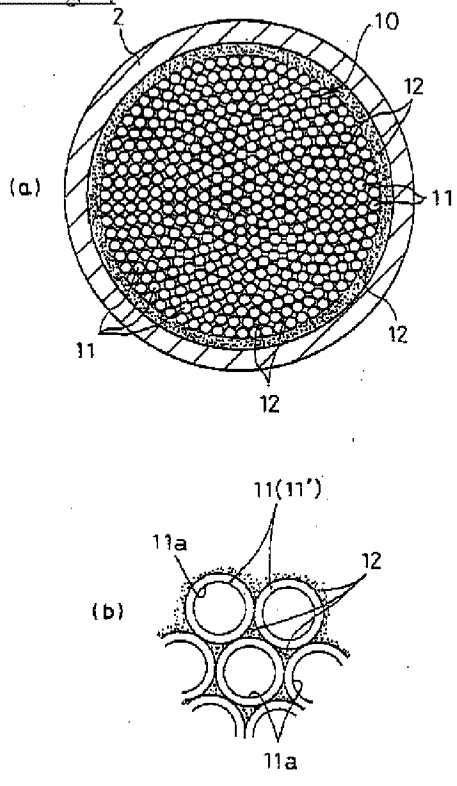
[Brief Description of the Drawings]
[Drawing 1] It is the explanatory view which made blood purifier the cross section.
[Drawing 2] It is drawing having shown the cutting plane of the hollow filament bundle in the edge of casing, and they are drawing in which (a) showed the whole cutting plane, and drawing in which (b) expanded and showed the part.
[Drawing 3] It is the flow chart which shows the outline of the production process of blood purifier.
[Drawing 4] It is drawing having shown aging of the amount of ultrafiltrations by the blood purification film with which the coating weight of a polyvinyl pyrrolidone differs.
[Description of Notations]
1 Blood Purifier
2 Casing
3 Impregnation Side Blood Port
4 Discharge Side Blood Port
5 Input of Dialysing Fluid
6 Exhaust Port of Dialysing Fluid
7 Inlet in Impregnation Side Blood Port
8 Exhaust Port in Discharge Side Blood Port
9 O Ring
10 Hollow Filament Bundle
11 Hollow Fiber (Blood Purification Film)
11' Hydrophobic hollow fiber
11a The internal surface of a hollow fiber
12 Sealing Material

DRAWINGS

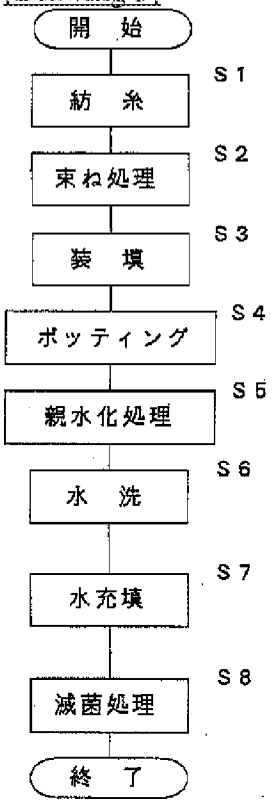
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Drawing 4]